CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial (CHAMPS)

Table of Activities by Visit

Visit #	Week/Timing of Visit	Clinical Evaluations[1]	Clinical Outcomes[2]	Hematology Panel (CBC)[3]	Adverse Events	Pregnancy Test	Chemistry Panel[4]	Urin-alysis	Central Labs[5]
		All Visits	*All Visits*	*All Visits*	*All Visits*	*Visits 1-15*	*Visits 1, 2, 6, 8, 10, 12, 14, 16*	*Visits 2,10,16*	*Visits 1, 2, 6, 8, 10, 15*
1	Week -1	X	X	X	X	X	X		X
2	Baseline (Visit 1 + 1-3 wks)	X	X	X	X	X	X	X	X
3	Week 2 ± 4 days	X	X	X	X	X			
4	Week 4 ± 4 days	X	X	X	X	X			
5	Week 6 ± 4 days	X	X	X	X	X			
6	**Week 8 ± 4 days**	**X**	**X**	**X**	**X**	**X**	**X**		**X**
7	Month 3 ± 8 days	X	X	X	X	X			
8	Month 4 ± 8 days	X	X	X	X	X	X		X
9	Month 5 ± 8 days	X	X	X	X	X			
10	Month 6 ± 8 days	X	X	X	X	X	X	X	X
11	Month 7 ± 8 days	X	X	X	X	X			
12	Month 8 ± 8 days	X	X	X	X	X	X		
13	Month 9 ± 8 days	X	X	X	X	X			
14	Mth 10 ± 8 days	X	X	X	X	X	X		
15	Mth 11 ± 8 days	X	X	X	X	X			X
16	Mth 12 ± 8 days	X	X	X	X		X	X	

Notes

- Visit 1 also includes electrophoresis and an HIV test.
- If a subject is transfused, electrophoresis is repeated as needed until the subject's Hb %A ≤ 10%.

1. Clinical Evaluations: brief physical exam to ensure general health
2. Clinical Outcomes: pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration. Cancer and neuroimaging collected at Visits 1, 2, 7, 10, 13, and 16.
3. Hematology Panel (CBC): Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC
4. Chemistry Panel: Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH
5. Central labs: for each visit with central labs, 3 vacutainers of blood will be sent to Boston (Brugnara) and 1 vacutainer of blood will be sent to Duke (Telen). Part of the specimen sent to the Boston (Brugnara) lab after Visit 1 will be forwarded to another central lab in Boston (Chui) for the α-Gene measurement. For the first 40 patients enrolled into the study, part of the specimen sent to Brugnara's lab will be sent to Italy (DeFranceschi) for additional laboratory analyses to examine red cell membrane kinase activity and oxygen damage to red cell membrane proteins.

CHAMPS Study Visit Checklist - All Study Visits

Comprehensive Sickle Cell Centers Clinical Trials Consortium

Visit One (Week –1)
- ❑ Electrophoresis*
- ❑ HIV Test
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Chemistry Panel
- ❑ Boston (Brugnara) Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke (Telen) Lab: 1 full 5-mL lavender vacutainer
- ❑ α gene measurement (part of the specimen sent to the Boston lab will be forwarded to another central lab for this value)

***If the subject is transfused, electrophoresis is repeated as needed until the subject's Hb %A ≤ 10%.**

Visit Two (Baseline: Visit 1 + 1-3 weeks)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Administer first dose of study drug
- ❑ Distribute Study Drug Log to Subject
- ❑ Chemistry Panel
- ❑ Urinalysis (U/A)
- ❑ Boston Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke Lab: 1 full 5-mL lavender vacutainer

Visit Three (Week 2 ± 4 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check

Visit Four (Week 4 ± 4 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug

Visit Five (Week 6 ± 4 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ CBC
- ❑ Pregnancy Test
- ❑ Toxicity Check

Visit Six (Week 8 ± 4 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug
- ❑ Chemistry Panel
- ❑ Boston Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke Lab: 1 full 5-mL lavender vacutainer

Visit Seven (Month 3 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug

Visit Eight (Month 4 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug
- ❑ Chemistry Panel
- ❑ Boston Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke Lab: 1 full 5-mL lavender vacutainer

Visit Nine (Month 5 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug

Visit 10 (Month 6 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug
- ❑ Chemistry Panel
- ❑ Urinalysis (U/A)
- ❑ Boston Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke Lab: 1 full 5-mL lavender vacutainer

Visit 11 (Month 7 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug

Visit 12 (Month 8 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug
- ❑ Chemistry Panel

Visit 13 (Month 9 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug

Visit 14 (Month 10 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer last monthly supply of study drug
- ❑ Chemistry Panel

Visit 15 (Month 11 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Boston Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke Lab: 1 full 5-mL lavender vacutainer

Visit 16 (Month 12 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Chemistry Panel
- ❑ Urinalysis (U/A)
- ❑ Toxicity Check

Note: Toxicity Visits, AEs for Painful Crisis, AEs, SAEs, Concomitant Medications, and Protocol Deviations are completed as needed.

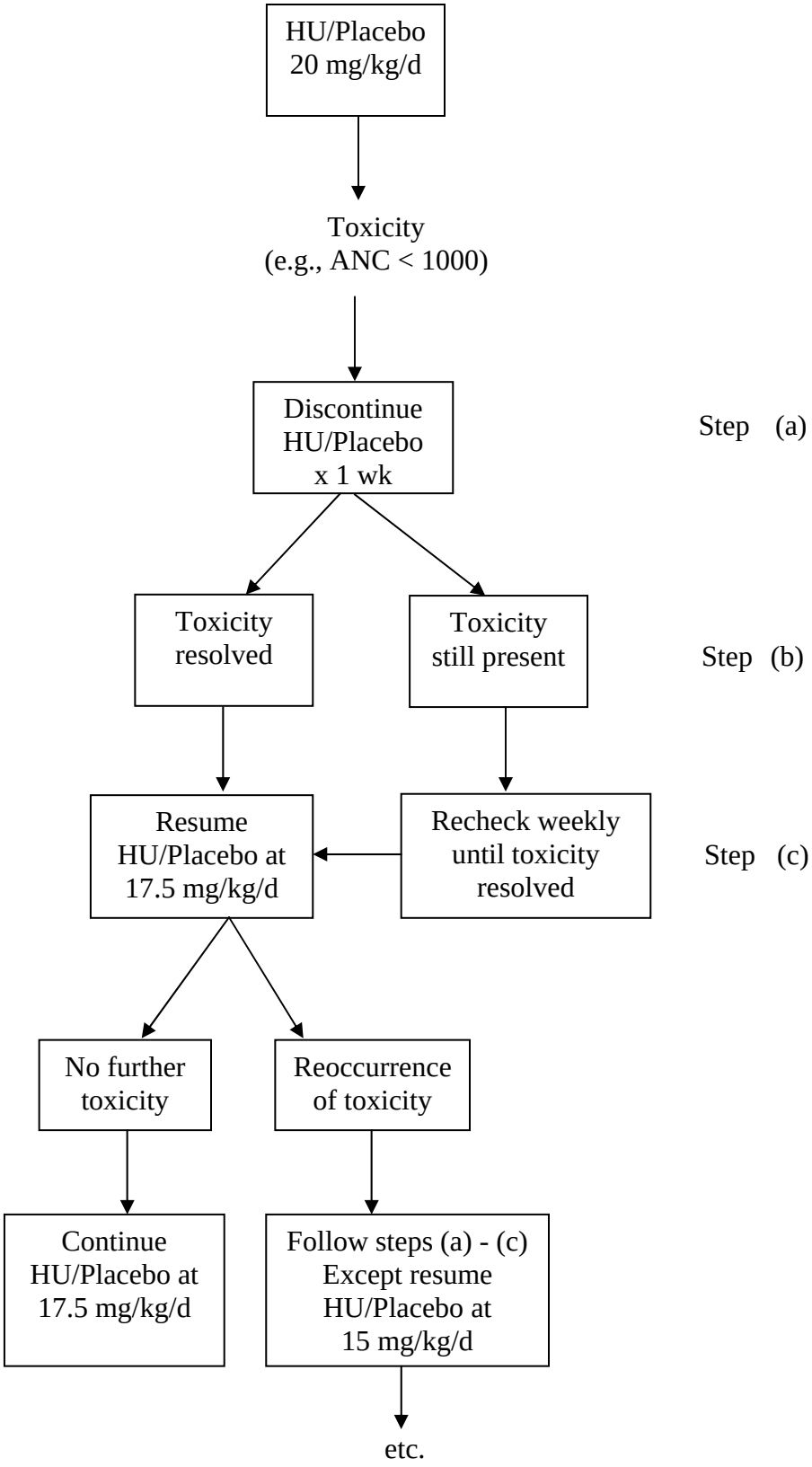
HYDROXYUREA (AND PLACEBO) DOSING AND DOSE ADJUSTMENT TABLE

Dose and # of caps refer to both HU and Placebo

caps = number of capsules per day. If more than one number, the subject should take the first number on the first day, the second on the 2nd day, etc, and then repeat. E.g. if dose is 2/1/1: 2 pills on Day One, 1 pill on Day Two, 1 pill on Day Three, then repeat (2 pills on Day Four, 1 pill on Day Five, 1 pill on Day Six, repeat).
Actual doses below are close approximations of the prescribed dose. Equivalent dosing may be used if necessary. E.g., a child with a dose of 500 mg who cannot swallow the large capsules may be given alternate a dose of 400 mg with a dose of 600 mg.

		20/mg/kg/d			17.5 mg/kg/d (1st Toxicity)			15 mg/kg/d (2nd Toxicity)			12.5 mg/kg/d (3rd Toxicity)		
Wt. (kg)	Wt. Range (kg)	HU/ Placebo Dose (mg)	500 mg (# caps)	200 mg (# caps)	Dose (mg)	500 mg (# caps)	200 mg (# caps)	Dose (mg)	500 mg (# caps)	200 mg (# caps)	Dose (mg)	500 mg (# caps)	200 mg (# caps)
15	12.6 - 17.5	300		2/1	262.5		2/1/1	225		2/1/1/1/1/1	187.5		1
20	17.6 - 22.5	400		2	350		2/2/2/1	300		2/1	250	1/0	
25	22.6 - 27.5	500	1		437.5		3/2/2/2	375		2	312.5		2/1
30	27.6 - 32.5	600		3	525	1		450		2	375		2
35	32.6 - 37.5	700	1	1	612.5		3	525	1		437.5		2
40	37.6 - 42.5	800		4	700	1	1	600		3	500	1	
45	42.6 - 47.5	900	1	2	787.5		4	675	1	1	562.5		3
50	47.6 - 52.5	1000	2		875		4	750	1	1	625		3
55	52.6 - 57.5	1100	1	3	962.5	1	2	825		4	687.5	1	1
60	57.6 - 62.5	1200	2	1	1050	2		900	1	2	750	1	1
65	62.6 - 67.5	1300	1	4	1137.5	1	3	975	2		812.5		4
70	67.6 - 72.5	1400	2	2	1225	2	1	1050	2		875	1	2
75	72.6 - 77.5	1500	3		1312.5	1	4	1125	1	3	937.5	1	2
80	77.6 - 82.5	1600	2	3	1400	2	2	1200	2	1	1000	2	
85	82.6 - 87.5	1700	3	1	1487.5	2	2	1275	1	4	1062	1	3
90	87.6 - 92.5	1800	2	4	1575	3		1350	2	2	1125	1	3
95	92.6 - 97.5	1900	3	2	1662.5	2	3	1425	2	2	1187.5	2	1
100	97.6 - 102.5	2000	4		1750	3	1	1500	3		1250	3/2	
105	102.6 - 107.5	2100	3	3	1837.5	2	4	1575	2	3	1312.5	1	4
110	107.6 - 112.5	2200	4	1	1925	3	2	1650	3	1	1375	2	2
115	112.6 - 117.5	2300	3	4	2012.5	4		1725	3	1	1437.5	2	2
120	117.6 - 122.5	2400	4	2	2100	3	3	1800	2	4	1500	3	
125	122.6 - 127.5	2500	5		2187.5	3	3	1875	3	2	1562.5	2	3

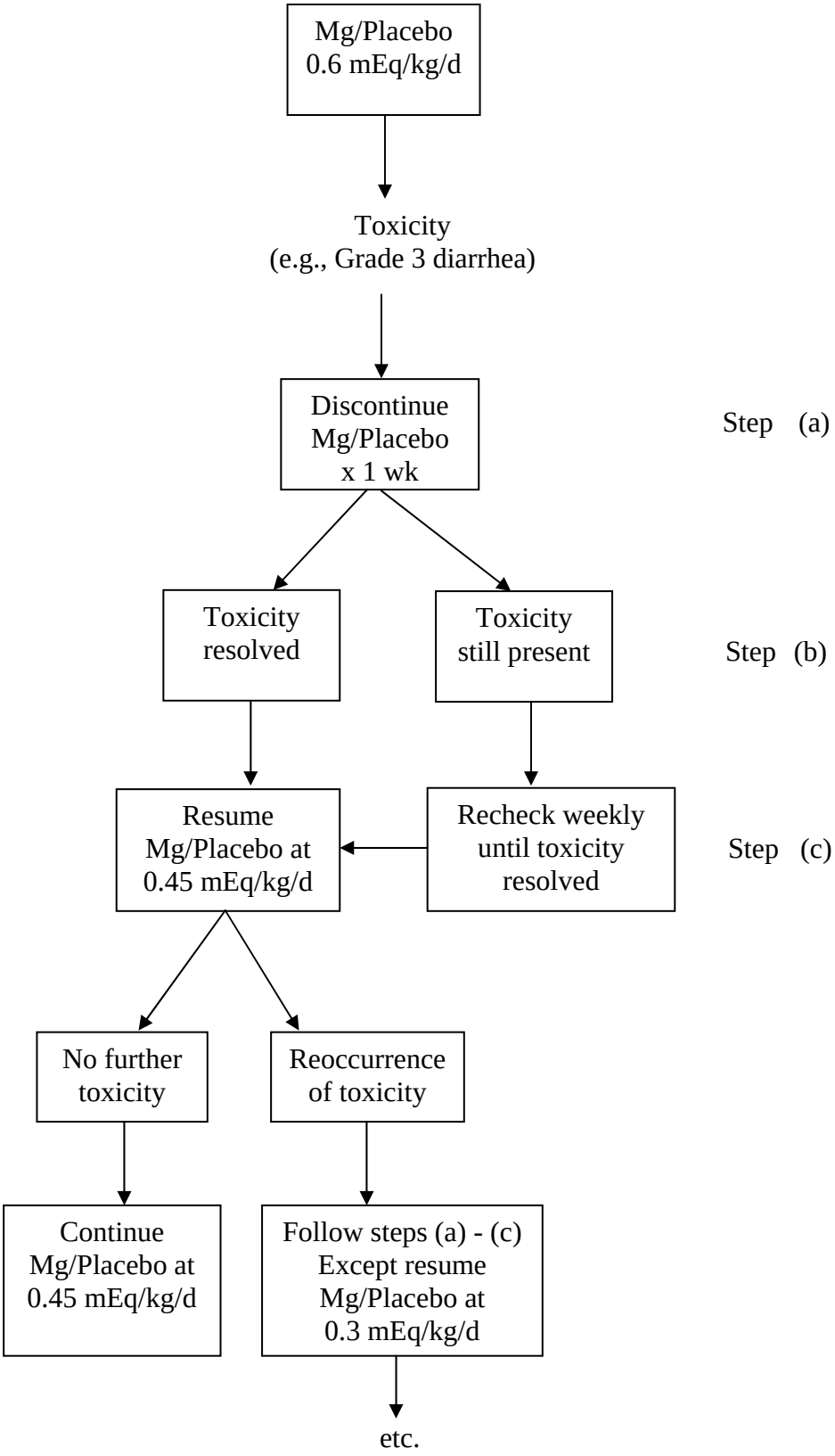
HU/Placebo Dose Modification for Toxicity



MAGNESIUM PIDOLATE (AND PLACEBO) DOSING & DOSE ADJUSTMENT TABLE

Wt. (kg)	Wt. Range (kg)	Initial Dose Mg Pidolate 0.3 mEq/kg BID		Dose after 1st Toxicity Mg Pidolate 0.225 mEq/kg BID		Dose after 2nd Toxicity Mg Pidolate 0.15 mEq/kg BID	
		(mEq)	(ml)	(mEq)	(ml)	(mEq)	(ml)
15	12.6 - 17.5	4.5	2.2	3.4	1.7	2.2	1.1
20	17.6 - 22.5	6.0	3.0	4.5	2.2	3.0	1.5
25	22.6 - 27.5	7.5	3.7	5.6	2.8	3.7	1.9
30	27.6 - 32.5	9.0	4.5	6.8	3.4	4.5	2.2
35	32.6 - 37.5	10.5	5.2	7.9	3.9	5.2	2.6
40	37.6 - 42.5	12.0	6.0	9.0	4.5	6.0	3.0
45	42.6 - 47.5	13.5	6.7	10.1	5.0	6.7	3.4
50	47.6 - 52.5	15.0	7.5	11.2	5.6	7.5	3.8
55	52.6 - 57.5	16.5	8.2	12.4	6.2	8.2	4.1
60	57.6 - 62.5	18.0	9.0	13.5	6.7	9.0	4.5
65	62.6 - 67.5	19.5	9.7	14.6	7.3	9.7	4.9
70	67.6 - 72.5	21.0	10.5	15.8	7.9	10.5	5.2
75	72.6 - 77.5	22.5	11.2	16.9	8.4	11.2	5.6
80	77.6 - 82.5	24.0	12.0	18.0	9.0	12.0	6.0
85	82.6 - 87.5	25.5	12.7	19.1	9.5	12.7	6.4
90	87.6 - 92.5	27.0	13.5	20.2	10.1	13.5	6.8
95	92.6 - 97.5	28.5	14.2	21.4	10.7	14.2	7.1
100	97.6 - 102.5	30.0	15.0	22.5	11.2	15.0	7.5
105	102.6 - 107.5	31.5	15.7	23.6	11.8	15.7	7.9
110	107.6 - 112.5	33.0	16.5	24.7	12.3	16.5	8.2
115	112.6 - 117.5	34.5	17.2	25.9	12.9	17.2	8.6
120	117.6 - 122.5	36.0	18.0	27.0	13.5	18.0	9.0
125	122.6 - 127.5	37.5	18.7	28.1	14.0	18.7	9.4

Mg/Placebo Dose Modification for Toxicity



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Specimen Collection and Shipping to the Duke Central Lab

June 13, 2007

1. Insert the needle into the rubber top of the 5-mL lavender-top vacutainer; collect blood into the vacutainer *until it is full*. Do NOT remove the rubber top of the vacutainer.
2. Place one barcode label on the vacutainer and place the duplicate barcode label on the "RhoLAB data collection sheet" (kept in the Subject Study Binder).
3. Log into RhoLAB, select the correct subject ID, and enter the barcode number on the vacutainer into the system via the barcode scanner.
4. Create a shipment within RhoLAB for the single vacutainer going to Duke and print a copy of the packing slip with the shipment ID # and shipment contents listed on it.
5. Insert the vacutainer into the Aqui-Pak absorbent pouch.
6. Roll up the Aqui-Pak and insert it into the small 95 kPa canister.
7. Place the small 95 kPa canister into the "Biohazard" ziplock bag and place it upright inside the foam cooler.
8. Fill one 12 x 12 ziplock bag with ice. Place this bag of ice into an empty ziplock bag (so that the ice is double-bagged).
9. Repeat Step 8.
10. Place the two bags of ice around the small, bagged 95 kPa canister.
11. Close the foam cooler and tape the packing slip generated by RhoLAB to the top of the foam cooler.
12. Log into Fedex.com using the username and password created by the SDMC for study coordinator or personnel responsible for shipping specimens to the central labs.
    - Select the Duke lab as the recipient of the 1 5-mL lavender-top vacutainer.
    - Check the box beside "Process return Label" under "More shipment details" section at the bottom.
13. Place the return label on top of the foam cooler.
14. Tape the outer cardboard box shut.
15. Apply the "UN3373 Biological Substance" label to outside of box.
16. Apply the "up arrow" labels to the opposite sides of box (narrow box ends).
17. Apply "biohazard" label to outside of box.
18. Apply "LAB OPEN IMMEDIATELY CHAMPS STUDY" label to the outside of the box.
19. Attach completed air bill to the top of the outside of the box and send to shipping area.

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Comprehensive Sickle Cell Centers
Clinical Trials Consortium

Specimen Collection and Shipping to the Boston Central Lab

June 13, 2007

1. Insert the needle into the rubber top of the 6-mL green-top vacutainer and collect blood into the vacutainer *until it is almost full*. Do NOT remove the rubber top of the vacutainer.
2. Insert the needle into the rubber top of EACH of the 10-mL purple-top vacutainers and collect blood approximately half way into the vacutainer. Do NOT remove the rubber top of the vacutainer.
3. Place one barcode label on each of the three vacutainers, place the duplicate barcode label on the "RhoLAB data collection sheet" (kept in the Subject Study Binder).
4. Log into RhoLAB, select the correct subject ID, and add the barcode numbers on each of the 3 vacutainers into the system via the barcode scanner (this will be done simultaneously with the 5-mL lavender vacutainer going to the Duke lab).
5. Create a shipment within RhoLAB for all three vacutainers going to Boston (Brugnara) and print a copy of the packing slip with the shipment ID # and shipment contents listed on it.
6. Insert each of the three vacutainers into one Aqui-Pak absorbent pouch.
7. Roll up the Aqui-Pak tube-over-tube and insert it into the small 95 kPa canister.
8. Place the small 95 kPa canister into Biohazard plastic bag and place it upright inside the foam cooler.
9. Fill one 12 x 12 ziplock bag with ice. Place this bag of ice into an empty ziplock bag (so that the ice is double-bagged).
10. Repeat Step 9.
11. Place the two bags of ice around the small 95 kPa canister.
12. Seal the foam cooler and tape the packing slip generated by RhoLAB to the top of the foam cooler.
13. Log into Fedex.com using the username and password created by the SDMC for study coordinator or personnel responsible for shipping specimens to the central labs.
    - Select the Boston (Brugnara) lab as the recipient of the 3 vacutainers.
    - Check the box beside "Process return Label" under "More shipment details" section at the bottom.
14. Place the return label on top of the foam cooler.
15. Tape the outer cardboard box shut.
16. Apply the "UN3373 Biological Substance" label to outside of box.
17. Apply the "up arrow" labels to the opposite sides of box (narrow box ends).
18. Apply the "biohazard" label to outside of box.
19. Apply the "LAB OPEN IMMEDIATELY HU-MG STUDY" label to the outside of the box.
20. Attach completed air bill to the outside of the box and send to the shipping area.

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CSCC
Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF and Completion Guidelines

Information about the forms

General information

- This study is using a remote data entry system. All data collected for this study will be entered into the CSCC's Electronic Data Capture System website. Data entry should be completed within one week of data collection.

Header information

- Some forms require the date of visit or assessment.
- The patient's CSCC ID number must be recorded on each individual CRF and will be pre-populated by the EDC system.

Dates

- Dates should be recorded in the following format: **dd/mmm/yy** (i.e., 22/JUN/06).
  Record leading zeros where applicable.
- If a complete date is unknown, record the date part(s) that are known and leave the rest blank. In some cases, a message will prompt the user to review the blank date or date parts. The user should override this validation check by clicking the override button. A comment explaining why the required lab value cannot be provided should be entered at this point.

Specific fields or blocks of information on a form that were not collected

- Leave the fields blank. In some cases, an override comment as described above will be required.

Numeric fields

- Rounding rules: If the digits to the right of the decimal in any number are greater than the number of boxes available for data entry of the number, then the value should be rounded to the correct number of places, using conventional rounding rules. Example: A lab value for hemoglobin of 12.06 g/dL will be entered as 12.1 g/dL and a lab value of 12.03 g/dL will be entered as 12.0 g/dL.

Source documentation

- Store all original study-related materials (case report forms, lab reports, etc.) in the subject's research record. File a copy in the subject's medical record and send copies to Rho or the DSMB as needed. If a case report form page was completed on paper before entering the data into the EDC system then store that CRF page in the subject's research record.
- Delete or completely mark out subject identifiers on all study materials. Be sure that the subject ID number is present.

CRF Completion Guidelines

Information about the EDC system

General information

- All information is to be entered via the CSCC's Electronic Data Capture (EDC) website.
- The subject ID and site header information will be automatically displayed when entering data in the EDC system.

To access the EDC system

Access will be granted to the EDC system once a site has all necessary documents to begin enrollment. To access the EDC system once a site has approval:

- Log on to the secure CSCC website.
- Choose "**CHAMPS"** from the list of studies on the right side of the screen.
- Under the heading "EDC Links", choose "Data Entry -> "**CHAMPS"**
- Open the subject for which you want to enter data by selecting subject ID number (for a subject already enrolled in this study), importing a subject from another CSCC study, or enrolling a new patient in the **CHAMPS** study.
- Select the page for which data is to be entered.
- Remember to log out when you are finished.

Corrections to data

- Open the page in the EDC system where the data was originally entered. Find the field and change the entry. Click the "Update" button at the bottom of the screen in order to submit corrections to the database.

Help documents

- Click the "EDC HELP" link in the gray navigation menu on the left side of the EDC screen for help navigating the EDC system.
- Each CRF page has a "Form completion help" link at the bottom of the page which contains information about completing that CRF page.

CHAMPS STUDY

Product Request Form

NOTE TO SITES : Fax completed form to Therapak at 626-357-5911 or email to RSchulze@Therapak.com

Shipper:
Therapak Corporation 1801 Highland Ave., Unit L Duarte, CA 91010 Phone: (626) 357-5900 Fax: (626) 357-5911 Email: RSchulze@Therapak.com

Rho Project Manager: *(Sites, please do not fax orders here)*
Name: Emily Kunka / Cathie Snyder
E-mail: Emily_Kunka@rhoworld.com cc: Cathie_Snyder@rhoworld.com
Phone: (919) 408-8000 x 585 / x 291
Fax: (919) 287-0126

Sponsor: NHLBI
Protocol Name: CHAMPS

Date Order Placed:
Date Needed at Site:

Ship To: Site ID:
Phone:

Shipping Method:
Freight:
Reference: Rho/CHAMPS/6203

ITEM #	ITEM DESCRIPTION	Max Order[1]	QTY.	LOT NO.	EXPIRATION
23027	Small 95 kPa Canister w/ Cap	3			
33622	Blood Sample Collection Kit[2]	6			
33623	Refrigerated (Wet Ice) Shipping Kit[3]	3			
33638	Accessory Kit[4] (Order this kit **OR** items with "CS" in the item #. Do not order both.)	2			
55521-CS	Mark-a-Dose Labels (order in increments of 100)	200			
79289-CS	5-mL Dosing Syringe (order in increments of 50)	100			
79290-CS	10-mL Dosing Syringe (order in increments of 25)	50			
79291-CS	20-mL Dosing Syringe (order in increments of 25)	50			
23013-CS	Press-In Bottle Adapters (for Mg bottles)	50			
57016-CS	7-Day Pill Dispensers	10			
50266	*Domestic Site Distribution Fee*				

1. Orders should not exceed the maximum order quantity. Contact Jason Davis at the SDMC if you need more than the maximum.

2. Blood Sample Collection Kit
   - ? One 6-mL green vacutainer
   - ? One 5-mL lavender vacutainer
   - ? Two 10-mL lavender vacutainer
   - ? Two 4-bay Aquipak (absorbent tube shuttle)
   - ? Eight 12 x 12 ziplock bags (to contain ice)
   - ? Two 6 x 9 ziplock bags (to contain plastic canister)
   - ? Two FedEx airbill pouches

3. Refrigerated (Wet Ice) Shipping Kit
   - ? One small foam cooler
   - ? One cardboard box for small cooler
   - ? One small canister (to place the 4-bay Aquipak enclosed in the 6 x 9 ziplock bag)
   - ? One Biohazard label
   - ? One UN3373 Diagnostic Specimens Label
   - ? Two Up Arrow Labels
   - ? One "LAB OPEN IMMEDIATELY CHAMPS STUDY"

4. Accessory Kit - Supply of all pharmacy accessories. Pharmacy accessories are identified above with "CS" in the item #.
   - ? 200 Mark-a-Dose Labels
   - ? 50 5-mL Dosing Syringes
   - ? 100 10-mL Dosing Syringes
   - ? 50 20-mL Dosing Syringes
   - ? 40 Press-In Bottle Adapters
   - ? 20 7-Day Pill Dispensers

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Comprehensive Sickle Cell Centers	**HU/Placebo Study Drug Dosing Log**	**Ongoing**
CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)		

CRF COMPLETION GUIDELINES

Item	Instructions
Initial Dose	Record the initial dose and the corresponding start and stop dates on the stand alone row.
Start Date	Record the start date to indicate when the new dose was initiated.
Stop Date	Record the stop date to indicate when that dose was stopped or changed.

Comprehensive Sickle Cell Centers	**HU/Placebo Study Drug Dosing Log**	**Ongoing**
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Initial Dose:

Dose (mg/kg/day)	**Dose** (mg)	**Start Date** DD MMM YYYY	**Stop Date** DD MMM YYYY
		_____ /_____/_____	_____ /_____/_____

Dose Changed or Interrupted:

→ If necessary, complete **AE Form** if dose was changed or interrupted.

→ Click the "Add" button **each time** HU/placebo dose is **changed or interrupted** and record the following information.

Dose (mg/kg/day)	**Dose** (mg)	**Start Date** DD MMM YYYY	**Stop Date** DD MMM YYYY
		_____ /_____/_____	_____ /_____/_____
		_____ /_____/_____	_____ /_____/_____
		_____ /_____/_____	_____ /_____/_____
		_____ /_____/_____	_____ /_____/_____
		_____ /_____/_____	_____ /_____/_____
		_____ /_____/_____	_____ /_____/_____
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		_____ /_____/_____	_____ /_____/_____
		_____ /_____/_____	_____ /_____/_____
		_____ /_____/_____	_____ /_____/_____
			ADD

Comprehensive Sickle Cell Centers	**Mg/Placebo Study Drug Dosing Log**	**Ongoing**
CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)		

CRF COMPLETION GUIDELINES

Item	Instructions
Initial Dose	Record the initial dose and the corresponding start and stop dates on the stand alone row.
Start Date	Record the start date to indicate when the new dose was initiated.
Stop Date	Record the stop date to indicate when that dose was stopped or changed.

Comprehensive Sickle Cell Centers	**Mg/Placebo Study Drug Dosing Log**	**Ongoing**
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Initial Dose:

Dose (mEq/kg B.I.D.)	**Dose (B.I.D.)** (mL)	**Start Date** DD MMM YYYY	**Stop Date** DD MMM YYYY
		_____ /_____ /_____	_____ /_____ /_____

Dose Changed or Interrupted:

→ If necessary, complete **AE Form** if dose was changed or interrupted.

→ Click the "Add" button **each time** Mg/placebo dose is **changed or interrupted** and record the following information.

Dose (mEq/kg B.I.D.)	**Dose (B.I.D.)** (mL)	**Start Date** DD MMM YYYY	**Stop Date** DD MMM YYYY
		_____ /_____ /_____	_____ /_____ /_____
		_____ /_____ /_____	_____ /_____ /_____
		_____ /_____ /_____	_____ /_____ /_____
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		_____ /_____ /_____	_____ /_____ /_____
		_____ /_____ /_____	_____ /_____ /_____
			ADD

Comprehensive Sickle Cell Centers	**HU/Placebo Study Drug Record**	**Ongoing**
CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)		

CRF COMPLETION GUIDELINES

Item	Instructions
Visit Number	Select the visit number to indicate at which visit the study drug was dispensed or check the unscheduled visit box to indicate that drug was dispensed at an unscheduled visit.
Start Date	Record the date to indicate when study drug was first taken.
Bottle Number	Record the bottle number indicated on the bottle label.
Capsule Type	Select '200 mg' or '500 mg'.
# Capsules Dispensed	Record the number of capsules dispensed as indicated on the bottle label.
Total Capsules Returned	Record the number of capsules that were returned for the bottle. Return information must correspond to the bottle number.
Not Returned	Check this box if, at the subject's final visit, the bottle has not been returned.
Return Date	Record the date to indicate when study drug bottle was returned.
Comments	Provide a comment to explain discrepancies in the number of pills returned and the number of pills taken. Provide a comment when no pills have been returned. Provide a comment if the initial start date is more than one day after the date for Visit 2 (i.e., initiation of study drug was delayed).

Comprehensive Sickle Cell Centers	**HU/Placebo Study Drug Record**	
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Randomization Number:** ☐☐☐☐	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Dispense							**Return**		
Visit # (drop-down) ☐☐ OR ☐ Unscheduled	**Start Date***	**Not Dispensed**	**Bottle Number**	**Prescribed Dose**	**Capsule Type**	**# Capsules Dispensed/ Bottle**	**Total Capsules Returned/ Bottle**	**Not Returned**	**Return Date**
	☐☐/☐☐☐/☐☐ Day Month Year		☐☐☐☐☐	☐☐☐☐.☐ mg	☐ 200 mg ☐ 500 mg	☐☐☐	☐☐☐	☐	☐☐/☐☐☐/☐☐ Day Month Year
		☐	☐☐☐☐☐		☐ 200 mg ☐ 500 mg	☐☐☐	☐☐☐	☐	☐☐/☐☐☐/☐☐ Day Month Year
							NOTE: Return Information must correspond to the bottle number recorded for this dispensing date.		

Comments

* If the initial start date is more than one day after the date for Visit 2, indicate why in the Comments field (i.e., initiation of study drug was delayed).

ADD

Comprehensive Sickle Cell Centers	**Mg/Placebo Study Drug Record**	**Ongoing**

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	Instructions
Visit Number	Select the visit number to indicate at which visit the study drug was dispensed or check the unscheduled visit box to indicate that drug was dispensed at an unscheduled visit.
Start Date	Record the date to indicate when study drug was first taken.
Bottle Number(s)	Record the bottle number(s) indicated on the bottle label.
Return Volume	For each bottle, record the return volume for the bottle and check 'fl. oz.' or 'mL'. Return information must correspond to the bottle number.
Not Returned	For each bottle, check this box if, at the subject's final visit, the bottle has not been returned.
Return Date	Record the date to indicate when study drug bottle was returned.
Comments	Provide a comment to explain discrepancies in the number of bottles/volume returned and the number of bottles/volume taken. Also provide a comment when no bottles/volume have been returned.

Comprehensive Sickle Cell Centers	**Mg/Placebo Study Drug Record**	
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Dispense					**Return**		
Visit # (drop-down)	**Start Date**	**Not Dispensed**	**Bottle Number**	**Prescribed Dose (B.I.D.)**	**Return Volume**	**Not Returned**	**Return Date**
☐☐ **OR** ☐ Unscheduled	☐☐/☐☐☐/☐☐ Day Month Year		☐☐☐☐☐	☐☐.☐ mL	☐☐☐ ☐ fl. oz. ☐ mL	☐	☐☐/☐☐☐/☐☐ Day Month Year
		☐	☐☐☐☐☐		☐☐☐ ☐ fl. oz. ☐ mL	☐	☐☐/☐☐☐/☐☐ Day Month Year
		☐	☐☐☐☐☐		☐☐☐ ☐ fl. oz. ☐ mL	☐	☐☐/☐☐☐/☐☐ Day Month Year

NOTE: Return Information must correspond to the bottle number recorded for this dispensing date.

Comments

ADD

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CHAMPS Study Checklist – Visit 1
(Week –1)

7-10 days before Visit 1: E-mail CHAMPS_labs@rhoworld.com noting that Visit 1 has been scheduled.

Visit One Tasks	Notes
❑ Informed Consent	Should be signed at Visit 1, as AEs are collected after the subject signs informed consent.
❑ Electrophoresis	
❑ HIV Test	
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration. Cancer and neuroimaging collected at Visits 1, 2, 7, 10, 13, and 16.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Chemistry Panel[2]	
❑ Collect specimens for Central Labs	▪ Boston Lab (Brugnara): 3 vacutainers - 2 half-full 10-mL lavender; 1 full 5-mL green - If short on blood, these vacutainers should be filled first ▪ Duke Lab (Telen): 1 full 5-mL lavender vacutainer
❑ Prepare specimens for shipping	▪ Enter Specimen IDs into RhoLAB and affix labels to the RhoLAB Specimen ID Tracker. ▪ Place a copy of the RhoLAB Packing List in Subject Binder ▪ See the "Study Help Documents" tab for instructions.
❑ CRFs and EDC	▪ Inclusion Criteria, Exclusion Criteria ▪ Screening - requires % of hyperdense cells from RhoLAB e-mail ▪ Physical Exam ▪ Medical History, Health History ▪ Hematology Labs, Chemistry Labs ▪ Pregnancy Test As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

FOLLOWING VISIT 1: Confirm eligibility per e-mail from RhoLAB (% hyperdense cells) AND local lab values.

If Eligible:
- Save RhoLAB e-mail (% hyperdense cells) in Subject Binder
- Schedule Visit 2. Enter date of Visit 2 on Visit 1 Screening CRF, & e-mail date to CHAMPS_labs@rhoworld.com 7-10 days before Visit 2.

Screen Failures:
- Complete the Screen Failure Log CRF.

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CHAMPS Source Document Worksheet for Visit 1

This worksheet is also used for the
Re-screening Visit 1 and 2nd Re-screening Visit 1

Date: _____ / _____ / _____ **Visit #:** 1 **CSCC ID:** _____

Inclusion Criteria

Q5 – Does the subject exhibit regular adherence with comprehensive care? □ Yes □ No

Q6 – Is the subject in a steady state and not having an acute complication of SCD? □ Yes □ No

Exclusion Criteria

Q3 – In the investigator's opinion, has the subject exhibited poor adherence with previous treatment regimens? □ Yes □ No

Q8 – Has the subject had treatment with an investigational drug in the last 3 months? □ Yes □ No

Q9 – Does the subject have any other chronic illness other than SCD that might affect his/her responsiveness to study drug? □ Yes □ No

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Medical History

*Complete this section **only** if the information was provided by the subject and cannot be verified in the medical record. For Re-screening Visits, simply update the information collected at Visit 1.*

Has the subject ever had or ever been diagnosed with: (if selected, enter year of 1st diagnosis and if present/occurred in the last year)

	Year of 1st Dx	Last Year?
□ Acute Chest Syndrome		□
□ Avascular Necrosis of Hip(s)		□
□ Avascular Necrosis of Shoulder(s)		□
□ Stroke		□
□ CNS – Other, specify		□
□ CNS – Other, specify		□
□ Hypersplenism		□
□ Leg Ulcers		□
□ Priapism □ Not Applicable		□
□ Retinopathy		□
□ Acute Splenic Sequestration		□

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet for Visit 1

This worksheet is also used for the
Re-screening Visit 1 and 2nd Re-screening Visit 1

Health History

In the past 12 months, has the subject had any pain crisis(es) at home for which there was no hospitalization or ED/day hospital/urgent care visit? *Only record information not present in the medical record! For Re-screening Visits, simply update the information collected at Visit 1.*

□ Yes □ No

If yes, how many pain crises:

- Were treated at home? _____
- Were treated in a clinic or doctor's office, not hospital? _____

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

RhoLAB Specimen ID Tracker

January 4, 2007

Subject ID Number _____

Visit Date _____

10-mL lavender vacutainer

10-mL lavender vacutainer

5-mL green vacutainer

5-mL lavender vacutainer

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Visit One

(Week 1)

- Inclusion Criteria
- Exclusion Criteria
- Screening
- Physical Exam
- Medical History
- Health History
- Hematology Labs
- Chemistry Labs
- Pregnancy Test
- Screen Failure Log for Visit 1

CRF COMPLETION GUIDELINES

Item	Instructions
Questions 3 and 6	Information obtained from *Health History* case report form (Visit 1, p. 7).
Note	Inclusion criterion #3 (Hb level 8-12.5 g/dL for children and adults), listed in the protocol, is incorporated into the CRF on the *Screening* page for this visit.

INCL

Comprehensive Sickle Cell Centers	**Inclusion Criteria**	**Visit 1** Page: 1 of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

For the subject to be eligible for this study, Questions 1 through 6 must be answered <u>Yes.</u>

1. Has the subject been diagnosed with Hb SC disease? ☐ Yes ☐ No

2. Is the subject 5 years of age or older? ☐ Yes ☐ No

3. Has the subject had at least one vaso-occlusive event (pain crisis[1], acute chest syndrome[2]) in the previous 12 months? ☐ Yes ☐ No

4. Has the subject/guardian signed an informed consent/assent form? ☐ Yes ☐ No

   Date of informed consent: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

5. Does the subject exhibit regular adherence with comprehensive care?[3] ☐ Yes ☐ No

6. Is the subject in a steady state and not having an acute complication of sickle cell disease [i.e., no hospitalization, pain event, or episode of acute chest syndrome within the past month (30 days)]? ☐ Yes ☐ No

[1] A pain crisis is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours, requires a visit to a hospital, Emergency Department, clinic, or provider's office, and is not explained except by sickle cell disease.

[2] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[3] A subject has exhibited regular adherence when he/she has consistently shown up for scheduled clinic visits and when he/she has been scheduled for at least one clinic visit per year.

CRF COMPLETION GUIDELINES

Item	Instructions
Question 1	Information obtained from the medical record.
Questions 4 and 5	Information obtained from the medical record. Mark 'No' if no test was performed in the previous month.
Question 6	Information obtained from pregnancy test administered at entry for this visit. This question must be answered 'Yes' or 'No' for all subjects.
Question 7	Information obtained from medical record and subject interview. For the purposes of this study, "extended period of time" is defined as 6 months of daily use, per the subject's self-report.
Questions 2, 8 and 9	Information obtained from medical record and subject interview.
Note	Additional exclusion criteria are listed in the protocol. These criteria are incorporated into the CRF on the *Screening* page for this visit. These criteria are listed in the protocol as: • #10 < 3% RBC with density > 41 g/dL (as measured by Advia 120) • #11 positive HIV test.

EXCL

For the subject to be eligible for this study, Questions 1 through 9 must be answered No.

1. Has the subject had any previous treatment with hydroxyurea within the last 3 months? ☐ Yes ☐ No

   Note: Subjects enrolled under Protocol Version 6.0 are excluded if EVER treated with hydroxyurea.

2. Has the subject had any treatment with magnesium within the past 3 months (including vitamins containing magnesium)? ☐ Yes ☐ No

3. In the investigator's opinion, has the subject exhibited poor adherence with previous treatment regimens? ☐ Yes ☐ No

4. Has the subject had hepatic dysfunction (SGPT > 2x upper limit of normal) within the past month? ☐ Yes ☐ No

5. Has the subject had renal dysfunction (creatinine ≥ 1.0 mg/dL, < 18.0 years of age; ≥ 1.2 mg/dL, ≥ 18.0 years of age) within the past month? ☐ Yes ☐ No

6. Is the subject pregnant? ☐ Yes ☐ No

7. Has the subject had ≥ 10 hospital admissions (overnight stays) for pain in the last 12 months, or has he/she been using narcotics daily for an extended period of time? [1] ☐ Yes ☐ No

8. Has the subject had treatment with an investigational drug in last 3 months? ☐ Yes ☐ No

9. Does the subject have any other chronic illness or disorder other than SCD that could adversely affect the subject's performance in the study (e.g., tuberculosis)? ☐ Yes ☐ No

[1] For the purposes of this study, "extended period of time" is defined as 6 months of daily use, per the subject's self-report.

CRF COMPLETION GUIDELINES

Item	Instructions
Expected Date of Next Visit	In an effort to estimate the number of samples the Duke (Telen) Central Lab must prepare to analyze red blood cell adhesion, study coordinators are asked to provide the expected date of next visit and email it to CHAMPS_labs@rhoworld.com.
Red Cell Density	Information obtained from the e-mail sent to the site from Boston (Brugnara) Central Lab via RhoLAB. If the email is not received, study coordinators with RhoLAB access can log into the system and view the results for current subjects.
Hemoglobin Level	Information obtained from Hematology Labs case report form for this visit.
HIV Status	If the subject has not had an HIV test within the last 12 months, one must be performed before he/she can continue in this study.
Hepatic Dysfunction	Screening SGPT level obtained from *Chemistry Labs* case report form for this visit.
Renal Dysfunction	Screening creatinine level obtained from *Chemistry Labs* case report form for this visit.

SCRE

Expected Date of Next Visit: *(Within 1 - 3 weeks of Visit 1)* ☐☐ / ☐☐☐ / ☐☐ → *Email date to CHAMPS_labs@rhoworld.com*
Day Month Year

1) Red Cell Density:

% Hyperdense cells ☐☐.☐ % *% hyperdense cells will be provided via an e-mail from RhoLAB.*

If the subject has ≥ 3 percent RBCs with density > 41 g/dL, he/she is eligible to continue in this study.

2) Hemoglobin Level:

Does the subject have a Hb level between 8 – 12.5 g/dL? ☐ Yes ☐ No

If the subject has a Hb level between 8 – 12.5 g/dL, he/she is eligible to continue in this study.

3) Hb A %:

Has the subject been transfused within the past 3 months? ☐ Yes ☐ No

→ **If yes**, is the subject's Hb A ≤ 10%? ☐ Yes ☐ No

If the subject has a Hb A % ≤ 10, he/she is eligible to continue in this study.

4) HIV Status: (*tested within the last 12 months)*

Date tested: ☐☐ / ☐☐☐ / ☐☐ Result: ☐ Negative ☐ Positive
Day Month Year

If the subject has a negative HIV test, he/she is eligible to continue in this study.

5) Hepatic Dysfunction:

Within the past month, has the subject had SGPT > 2x the upper limit of normal? ☐ Yes ☐ No

Screening SGPT level (U/L) ☐☐☐☐ Local lab upper limit of normal (U/L) ☐☐☐☐

If the subject has not had SGPT > 2x upper limit of normal within the past month, he/she is eligible to continue in this study.

6) Renal Dysfunction:

Within the past month has subject had creatinine ≥ 1.0 mg/dL (if under age 18.0 years) or ≥ 1.2 mg/dL (if age 18.0 years or above)? ☐ Yes ☐ No

Screening creatinine level (mg/dL) ☐☐.☐ Local lab upper limit of normal (mg/dL) ☐☐.☐

If the subject has not had creatinine ≥ 1.0 mg/dL (if under age 18.0 years) or ≥ 1.2 mg/dL (if 18.0 years or above) within the past month, he/she is eligible to continue in this study.

Demographics

Date of Birth: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Gender: ☐ Male ☐ Female

Hemoglobinopathy

Date of Results: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

S (%) ☐☐.☐

C (%) ☐☐.☐

A (%) ☐☐.☐

A2 (%) ☐.☐

F (%) ☐☐.☐

Other (%) ☐☐.☐

Include the decimal if provided on the lab report (e.g., 24.6 or 24.0).

If no decimal is provided on the lab report, leave the last box empty (e.g., 24); do not add a zero.

Other, specify type of electrophoresis: _____

If this subject has been re-screened AND had a transfusion within the last 3 months, please repeat the hemoglobin electrophoresis and enter the results here; these results will replace the data that were previously entered.

Physical Exam

☐ Not Done → Specify_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*

(at the greatest distance below the left costal margin)

3) Does the subject have any skin lesions? ☐ Yes ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Is the subject taking any medication? ☐ Yes ☐ No

→ *If **yes**, record information on the Concomitant Medications CRF.*

→ *Be sure to check "Pre-existing" on the Concomitant Medications CRF.*

[1] Weight should be measured with the subject standing still, wearing light clothing (such as a paper exam gown), and no shoes.

Information to be determined by patient interview and review of medical records.

Medical Conditions

1. Is the subject enrolled in the C-Data study? ☐ Yes ☐ No

2. Check "Yes", "No", or "Unknown" to indicate whether the subject has been diagnosed with any of the following conditions.

→ For any condition marked "Yes" provide the "Year of First Diagnosis." Also, indicate whether the condition is currently present or occurred in the past year.

Yes	Year of First Diagnosis	No	Unknown	Condition	If yes, Present/ Occurred in past year?
☐	_____	☐	☐	(Pulmonary) Acute Chest Syndrome	☐
☐	_____	☐	☐	(Muscular, Skeletal, Skin) Avascular Necrosis of Hip(s)	☐
☐	_____	☐	☐	(Muscular, Skeletal, Skin) Avascular Necrosis of Shoulder(s)	☐
☐	_____	☐	☐	(CNS) Stroke	☐
				(CNS) Other	
	_____			→ Specify: _____	☐
	_____			→ Specify: _____	☐
☐	_____	☐	☐	(Splenic) Hypersplenism	☐
☐	_____	☐	☐	(Muscular, Skeletal, Skin) Leg Ulcers	☐
☐	_____	☐	☐	(Renal/Genitourinary) Priapism ☐ N/A, female subject	☐
☐	_____	☐	☐	(Ocular) Retinopathy	☐
☐	_____	☐	☐	(Anemia) Acute Splenic Sequestration	☐

If this subject has been re-screened, please update this form as appropriate to reflect any changes to the subject's medical history since the last time the subject was screened.

Comprehensive Sickle Cell Centers	**Medical History**	**Visit 1** Page: 6 of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Information to be determined by patient interview and review of medical records.

Cancer

Has the subject ever had or ever been diagnosed with cancer? ☐ Yes ☐ No

→ If yes, list the type(s) of cancer below. For each type listed provide year of first diagnosis and indicate whether present in the last year.

Type of Cancer	Year of First Diagnosis	Present in Last Year?
		☐ Yes ☐ No
		☐ Yes ☐ No
		☐ Yes ☐ No

Neuroimaging

In the past year, has **neuroimaging** revealed any significant abnormal findings? ☐ Yes ☐ No ☐ Not Done

→ **If yes** click the ADD button and, record details for each test/type.

Date of test: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Type of test*: ☐ MRI ☐ MRA ☐ CT ☐ Cerebral angiography ☐ Other, specify ____________

Briefly describe the findings: ____

____

Date of test: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Type of test*: ☐ MRI ☐ MRA ☐ CT ☐ Cerebral angiography ☐ Other, specify ____________

Briefly describe the findings: ____

____

Date of test: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Type of test*: ☐ MRI ☐ MRA ☐ CT ☐ Cerebral angiography ☐ Other, specify ____________

Briefly describe the findings: ____

____

* Information about "**types of tests**" may be downloaded from the CHAMPS web page on the CSCC website.

ADD

If this subject has been re-screened, please update this form as appropriate to reflect any changes to the subject's medical history since the last time the subject was screened.

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click "ADD" to enter data for each event that has occurred in the past year. • If a single event was treated in multiple locations, check the box corresponding to each location and provide all applicable dates. Do not click the 'ADD' button for each location. • Check all reasons that apply. Do not complete the specify field unless 'Other' is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as "reasons" may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject's self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject's self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter "yes" the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason "unknown" or "date part unknown" when prompted.

HLHX

All questions relate to events in the past 12 months.

1) Has the subject had acute events that led to a visit to physician's office/clinic/emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event.

Treatment Location:

Date of Encounter:

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

[1] Complete AE and/or SAE forms for each reason IF the event occurred after the informed consent form was signed.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

If this subject has been re-screened, please update this form as appropriate to reflect any acute events or transfusions since the last time the subject was screened.

Comments for page _____

This question relates to events <u>in the past 12 months</u>.

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, click the "ADD" button and record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis
☐ Exacerbation of anemia due to splenic sequestration
☐ ACS
☐ Other complication of sickle cell disease (CNS event, priapism, AVN)
☐ Preparation for anesthesia
☐ Other, specify _____

ADD

If this subject has been re-screened, please update this form as appropriate to reflect any acute events or transfusions since the last time the subject was screened.

Comments for page _____

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CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Hemoglobin	Hemoglobin must be between 8.0 and 12.5 g/dL at study entry. Use this value to answer the second question on the *Screening* CRF (Does the subject have an Hb level between 8.0 – 12.5 g/dL?)

HEMA

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic	☐☐.☐
OR	
ARC (x10^3/mm^3)	☐☐☐
ANC (/mm^3)	☐☐☐☐☐

→ Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	• For subjects < 18 years of age, creatinine must be ≤ 1.0 mg/dL. • For subjects ≥ 18, creatinine must be ≤ 1.2 mg/dL. • If this criteria is not met, the subject is not eligible to be in the study.
SGPT	• SGPT must be < 2x the upper limit of normal at study entry. • If this criteria is not met, the subject is not eligible to be in the study.

CHEM

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

TEST	VALUE
Sodium (mmol/L)	☐☐☐
Potassium (mmol/L)	☐.☐
Chloride (mmol/L)	☐☐☐
CO_2 (mmol/L)	☐☐.☐
BUN (mg/dL)	☐☐☐
Creatinine (mg/dL)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
SGPT/ALT (U/L)	☐☐☐☐
Alk phosphatase (U/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (g/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (U/L)	☐☐☐☐

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

PREG

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
General	This form should be completed the ***first time*** a subject discontinues prior to receiving study drug. If the subject discontinues prior to completing Visit 1, complete only this log. If the subject discontinues after completing Visit 1, complete this log and all Visit 1 forms.
Date of last contact	Record the date on which the subject was last contacted for a study related reason.
Primary reason subject not enrolled	Select the primary reason the subject was not enrolled. Specify if applicable.
Complete V1?	Check “Yes” or “No”. If “No,” provide the Date of Informed Consent. If “Yes,” complete all CRFs for Visit 1.
Eligible for Re-screening Visit?	Check “Yes” or “No”. If “No,” specify the reason the subject is not eligible.

Comprehensive Sickle Cell Centers	**Screen Failure Log for Visit 1**	**Visit 1** Page: 11 of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

This form is to be completed the *first time* the subject discontinues prior to receiving study drug.

Date of last study related contact: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Primary Reason the subject will not be enrolled: (Check only one.)

☐ In the investigator's opinion, the subject's health, safety and/or well-being would be threatened by participation in the study.

☐ Subject lost to follow-up.

☐ Subject or subject's legal representative requested to withdraw. ***Specify:*** _____

☐ Subject did not meet inclusion/exclusion criteria.

Is subject no longer in steady state after previously meeting inclusion/exclusion criteria? ☐ Yes ☐ No

→ **If Yes,** check all that apply and complete the Adverse Event forms.

☐ Subject experienced one or more vaso-occlusive crises

☐ Subject experienced one or more non-vaso-occlusive sickle events

☐ Subject experienced one or more non-sickle related events

☐ Other Reason, ***Specify:*** _____

Did subject complete Visit 1? ☐ Yes ☐ No

→ **If no,** please provide the Date of Informed Consent.

Date of Informed Consent: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

→ **If yes,** be sure to complete all Visit 1 CRFs.

Is this subject eligible for a Re-screening Visit? ☐ Yes ☐ No

→ **If no,** specify the reason the subject is not eligible.

Reason, ***Specify:*** _____

Investigator's Statement:

I have reviewed the data entries within this CRF and, to the best of my knowledge, the data represent a complete and accurate record of the subject's participation in the study.

PI signature: _____ Signature Date: ☐☐ / ☐☐☐ / ☐☐☐☐
Day Month Year

CHAMPS Study Checklist – Re-Screening - Visit 1 (If Applicable)

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

7-10 days before Visit: E-mail CHAMPS_labs@rhoworld.com noting that Re-Screening Visit 1 has been scheduled.

Visit One Tasks	Notes
❑ Informed Consent	If applicable
❑ Electrophoresis	Does not have to be repeated unless subject has been transfused since the previous electrophoresis, and within 3 months of the re-screening visit.
❑ HIV Test	Need result within the last 12 months, may not need to re-test.
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Chemistry Panel[2]	
❑ Collect specimens for Central Labs	▪ Boston Lab (Brugnara): 3 vacutainers - 2 half-full 10-mL lavender; 1 full 5-mL green - If short on blood, these vacutainers should be filled first ▪ Duke Lab (Telen): 1 full 5-mL lavender vacutainer
❑ Prepare specimens for shipping	▪ Enter Specimen IDs into RhoLAB and affix labels to the RhoLAB Specimen ID Tracker. ▪ Place a copy of the RhoLAB Packing List in Subject Binder ▪ See the "Study Help Documents" tab for instructions.
❑ CRFs and EDC	▪ Inclusion Criteria, Exclusion Criteria ▪ Screening - requires % of hyperdense cells from RhoLAB e-mail ▪ Physical Exam ▪ Medical History, Health History – Update the Medical and Health History CRFs from Visit 1 to reflect any changes to the subject's medical history since the last time the subject was screened. ▪ Hematology Labs, Chemistry Labs ▪ Pregnancy Test As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

FOLLOWING VISIT: Confirm eligibility per e-mail from RhoLAB (% hyperdense cells) AND local lab values.

If Eligible:

- Save RhoLAB e-mail (% hyperdense cells) in Subject Binder
- Schedule Visit 2. Enter date of Visit 2 on the Re-Screening-Visit 1 Screening CRF, & e-mail date to CHAMPS_labs@rhoworld.com 7-10 days before Visit 2.

Screen Failures:

- Complete the Screen Failure Log CRF.

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CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet for Visit 1

This worksheet is also used for the
Re-screening Visit 1 and 2nd Re-screening Visit 1

Date: _____ / _____ / _____ **Visit #:** 1 **CSCC ID:** _____

Inclusion Criteria

Q5 – Does the subject exhibit regular adherence with comprehensive care? □ Yes □ No

Q6 – Is the subject in a steady state and not having an acute complication of SCD? □ Yes □ No

Exclusion Criteria

Q3 – In the investigator's opinion, has the subject exhibited poor adherence with previous treatment regimens? □ Yes □ No

Q8 – Has the subject had treatment with an investigational drug in the last 3 months? □ Yes □ No

Q9 – Does the subject have any other chronic illness other than SCD that might affect his/her responsiveness to study drug? □ Yes □ No

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Medical History

*Complete this section **only** if the information was provided by the subject and cannot be verified in the medical record. For Re-screening Visits, simply update the information collected at Visit 1.*

Has the subject ever had or ever been diagnosed with: (if selected, enter year of 1st diagnosis and if present/occurred in the last year)

	Year of 1st Dx	Last Year?
□ Acute Chest Syndrome		□
□ Avascular Necrosis of Hip(s)		□
□ Avascular Necrosis of Shoulder(s)		□
□ Stroke		□
□ CNS – Other, specify		□
□ CNS – Other, specify		□
□ Hypersplenism		□
□ Leg Ulcers		□
□ Priapism □ Not Applicable		□
□ Retinopathy		□
□ Acute Splenic Sequestration		□

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet for Visit 1

This worksheet is also used for the
Re-screening Visit 1 and 2nd Re-screening Visit 1

Health History

In the past 12 months, has the subject had any pain crisis(es) at home for which there was no hospitalization or ED/day hospital/urgent care visit? *Only record information not present in the medical record! For Re-screening Visits, simply update the information collected at Visit 1.*

□ Yes □ No

If yes, how many pain crises:

- Were treated at home? _____
- Were treated in a clinic or doctor's office, not hospital? _____

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Re-screening - Visit 1 (if applicable)

- Inclusion Criteria
- Exclusion Criteria
- Screening (Re-screen)
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Pregnancy Test
- Screen Failure Log for Re-screening – Visit 1

- **The Medical Health History CRF and the Health History CRF are not repeated here; please update the forms that were submitted with the original Visit 1 CRFs.**
- **If this subject has been re-screened AND been transfused within the last 3 months, please repeat the hemoglobin electrophoresis and enter the date of results and results in the Hemoglobinopathy section of the Visit 1 Screening CRF (page 3b of 11); this will replace the data that were previously entered.**

CRF COMPLETION GUIDELINES

Item	Instructions
Questions 3 and 6	Information obtained from *Health History* case report form (Visit 1, p. 7).
Note	Inclusion criterion #3 (Hb level 8-12.5 g/dL for children and adults), listed in the protocol, is incorporated into the CRF on the *Screening* page for this visit.

INCL

Comprehensive Sickle Cell Centers	**Inclusion Criteria**	**Re-screening – Visit 1** Page: 1 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

For the subject to be eligible for this study, Questions 1 through 6 must be answered <u>Yes.</u>

1. Has the subject been diagnosed with Hb SC disease?	☐ Yes	☐ No
2. Is the subject 5 years of age or older?	☐ Yes	☐ No
3. Has the subject had at least one vaso-occlusive event (pain crisis[1], acute chest syndrome[2]) in the previous 12 months?	☐ Yes	☐ No
4. Has the subject/guardian signed an informed consent/assent form?	☐ Yes	☐ No
Date of informed consent: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)		
5. Does the subject exhibit regular adherence with comprehensive care?[3]	☐ Yes	☐ No
6. Is the subject in a steady state and not having an acute complication of sickle cell disease [i.e., no hospitalization, pain event, or episode of acute chest syndrome within the past month (30 days)]?	☐ Yes	☐ No

[1] A pain crisis is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours, requires a visit to a hospital, Emergency Department, clinic, or provider's office, and is not explained except by sickle cell disease.

[2] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[3] A subject has exhibited regular adherence when he/she has consistently shown up for scheduled clinic visits and when he/she has been scheduled for at least one clinic visit per year.

CRF COMPLETION GUIDELINES

Item	Instructions
Question 1	Information obtained from the medical record.
Questions 4 and 5	Information obtained from the medical record. Mark 'No' if no test was performed in the previous month.
Question 6	Information obtained from pregnancy test administered at entry for this visit. This question must be answered 'Yes' or 'No' for all subjects.
Question 7	Information obtained from medical record and subject interview. For the purposes of this study, "extended period of time" is defined as 6 months of daily use, per the subject's self-report.
Questions 2, 8 and 9	Information obtained from medical record and subject interview.
Note	Additional exclusion criteria are listed in the protocol. These criteria are incorporated into the CRF on the *Screening* page for this visit. These criteria are listed in the protocol as: • #10 < 3% RBC with density > 41 g/dL (as measured by Advia 120) • #11 positive HIV test.

EXCL

For the subject to be eligible for this study, Questions 1 through 9 must be answered No.

1. Has the subject had any previous treatment with hydroxyurea within the last 3 months? **Note: Subjects enrolled under Protocol Version 6.0 are excluded if EVER treated with hydroxyurea.**	☐ Yes	☐ No
2. Has the subject had any treatment with magnesium within the past 3 months (including vitamins containing magnesium)?	☐ Yes	☐ No
3. In the investigator's opinion, has the subject exhibited poor adherence with previous treatment regimens?	☐ Yes	☐ No
4. Has the subject had hepatic dysfunction (SGPT > 2x upper limit of normal) within the past month?	☐ Yes	☐ No
5. Has the subject had renal dysfunction (creatinine ≥ 1.0 mg/dL, < 18.0 years of age; ≥ 1.2 mg/dL, ≥ 18.0 years of age) within the past month?	☐ Yes	☐ No
6. Is the subject pregnant?	☐ Yes	☐ No
7. Has the subject had ≥ 10 hospital admissions (overnight stays) for pain in the last 12 months, or has he/she been using narcotics daily for an extended period of time? [1]	☐ Yes	☐ No
8. Has the subject had treatment with an investigational drug in last 3 months?	☐ Yes	☐ No
9. Does the subject have any other chronic illness or disorder other than SCD that could adversely affect the subject's performance in the study (e.g., tuberculosis)?	☐ Yes	☐ No

[1] For the purposes of this study, "extended period of time" is defined as 6 months of daily use, per the subject's self-report.

CRF COMPLETION GUIDELINES

Item	Instructions
Expected Date of Next Visit	In an effort to estimate the number of samples the Duke (Telen) Central Lab must prepare to analyze red blood cell adhesion, study coordinators are asked to provide the expected date of next visit and email it to CHAMPS_labs@rhoworld.com.
Red Cell Density	Information obtained from the e-mail sent to the site from Boston (Brugnara) Central Lab via RhoLAB. If the email is not received, study coordinators with RhoLAB access can log into the system and view the results for current subjects.
Hemoglobin Level	Information obtained from Hematology Labs case report form for this visit.
HIV Status	If the subject has not had an HIV test within the last 12 months, one must be performed before he/she can continue in this study.
Hepatic Dysfunction	Screening SGPT level obtained from *Chemistry Labs* case report form for this visit.
Renal Dysfunction	Screening creatinine level obtained from *Chemistry Labs* case report form for this visit.

SCR2

Comprehensive Sickle Cell Centers	**Screening (Re-screen)**	**Re-screening – Visit 1** Page: 3a of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Expected Date of Next Visit: ☐☐ / ☐☐☐ / ☐☐ → *Email date to CHAMPS_labs@rhoworld.com*
(Within 1 - 3 weeks of Visit 1)
Day Month Year

1) Red Cell Density:

% Hyperdense cells ☐☐.☐ % *% hyperdense cells will be provided via an e-mail from RhoLAB.*

If the subject has ≥ 3 percent RBCs with density > 41 g/dL, he/she is eligible to continue in this study.

2) Hemoglobin Level:

Does the subject have a Hb level between 8 – 12.5 g/dL? ☐ Yes ☐ No

If the subject has a Hb level between 8 – 12.5 g/dL, he/she is eligible to continue in this study.

3) Hb A %:

Has the subject been transfused within the past 3 months? ☐ Yes ☐ No

→ **If yes**, is the subject's Hb A ≤ 10%? ☐ Yes ☐ No

If the subject has a Hb A % ≤ 10, he/she is eligible to continue in this study.

4) HIV Status: (*tested within the last 12 months)*

Date tested: ☐☐ / ☐☐☐ / ☐☐ Result: ☐ Negative ☐ Positive
Day Month Year

If the subject has a negative HIV test, he/she is eligible to continue in this study.

5) Hepatic Dysfunction:

Within the past month, has the subject had SGPT > 2x the upper limit of normal? ☐ Yes ☐ No

Screening SGPT level (U/L) ☐☐☐☐ Local lab upper limit of normal (U/L) ☐☐☐☐

If the subject has not had SGPT > 2x upper limit of normal within the past month, he/she is eligible to continue in this study.

6) Renal Dysfunction:

Within the past month has subject had creatinine ≥ 1.0 mg/dL (if under age 18.0 years) or ≥ 1.2 mg/dL (if age 18.0 years or above)? ☐ Yes ☐ No

Screening creatinine level (mg/dL) ☐☐.☐ Local lab upper limit of normal (mg/dL) ☐☐.☐

If the subject has not had creatinine ≥ 1.0 mg/dL (if under age 18.0 years) or ≥ 1.2 mg/dL (if 18.0 years or above) within the past month, he/she is eligible to continue in this study.

Physical Exam

☐ Not Done → Specify_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*

(at the greatest distance below the left costal margin)

3) Does the subject have any skin lesions? ☐ Yes ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Is the subject taking any medication? ☐ Yes ☐ No

→ *If **yes**, record information on the Concomitant Medications CRF.*

→ *Be sure to check "Pre-existing" on the Concomitant Medications CRF.*

[1] Weight should be measured with the subject standing still, wearing light clothing (such as a paper exam gown), and no shoes.

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CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Hemoglobin	Hemoglobin must be between 8.0 and 12.5 g/dL at study entry. Use this value to answer the second question on the *Screening* CRF (Does the subject have an Hb level between 8.0 – 12.5 g/dL?)

HEMA

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Re-screening – Visit 1** Page: 5 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (/mm^3)	☐☐☐☐☐

→ Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	• For subjects < 18 years of age, creatinine must be ≤ 1.0 mg/dL. • For subjects ≥ 18, creatinine must be ≤ 1.2 mg/dL. • If this criteria is not met, the subject is not eligible to be in the study.
SGPT	• SGPT must be < 2x the upper limit of normal at study entry. • If this criteria is not met, the subject is not eligible to be in the study.

CHEM

Comprehensive Sickle Cell Centers	**Chemistry Labs**	**Re-screening – Visit 1** Page: 6 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Sodium (mmol/L)	☐☐☐
Potassium (mmol/L)	☐.☐
Chloride (mmol/L)	☐☐☐
CO_2 (mmol/L)	☐☐.☐
BUN (mg/dL)	☐☐☐
Creatinine (mg/dL)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
SGPT/ALT (U/L)	☐☐☐☐
Alk phosphatase (U/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (g/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (U/L)	☐☐☐☐

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

PREG

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
General	This form should be completed the ***second time*** a subject discontinues prior to receiving study drug. If the subject discontinues prior to completing the Re-screening Visit, complete only this log. If the subject discontinues after completing the Re-screening Visit, complete this log and all Re-screening Visit forms.
Date of last contact	Record the date on which the subject was last contacted for a study related reason.
Primary reason subject not enrolled	Select the primary reason the subject was not enrolled. Specify if applicable.
Complete Re-screening?	Check "Yes" or "No". If "No," provide the Date of Informed Consent. If "Yes," complete all CRFs for the Re-screening Visit. Also update as appropriate, the two Medical History forms and the Health History form under the Visit 1 EDC link.
Eligible for 2nd Re-screening Visit?	Check "Yes" or "No". If "No," specify the reason the subject is not eligible.

Comprehensive Sickle Cell Centers	**Screen Failure Log for Re-screening – Visit 1**	**Re-screening – Visit 1** Page: 8 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

This form is to be completed the *second time* the subject discontinues prior to receiving study drug.

Date of last study related contact: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Primary Reason the subject will not be enrolled: (Check only one.)

☐ In the investigator's opinion, the subject's health, safety and/or well-being would be threatened by participation in the study.

☐ Subject lost to follow-up.

☐ Subject or subject's legal representative requested to withdraw. ***Specify:*** _____

☐ Subject did not meet inclusion/exclusion criteria.

Is subject no longer in steady state after previously meeting inclusion/exclusion criteria? ☐ Yes ☐ No

→ **If Yes,** check all that apply and complete the Adverse Event forms.

☐ Subject experienced one or more vaso-occlusive crises

☐ Subject experienced one or more non-vaso-occlusive sickle events

☐ Subject experienced one or more non-sickle related events

☐ Other Reason, ***Specify:*** _____

Did subject complete the Re-screening Visit? ☐ Yes ☐ No

→ **If no,** please provide the Date of Informed Consent at the Re-screening Visit.

Date of Informed Consent: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

→ **If yes,** be sure to complete the Re-screening CRFs. Also update as appropriate, the <u>two Medical History</u> **forms and the <u>Health History</u> form under the Visit 1 EDC link.**

Is this subject eligible for the 2nd Re-screening Visit? ☐ Yes ☐ No

→ **If no,** specify the reason the subject is not eligible.

Reason, ***Specify:*** _____

Investigator's Statement:

I have reviewed the data entries within this CRF and, to the best of my knowledge, the data represent a complete and accurate record of the subject's participation in the study.

PI signature: _____ Signature Date: ☐☐ / ☐☐☐ / ☐☐☐☐
Day Month Year

CHAMPS Study Checklist – 2nd Re-Screening - Visit 1 (If Applicable)

Comprehensive Sickle Cell Centers Clinical Trials Consortium

7-10 days before Visit: E-mail CHAMPS_labs@rhoworld.com noting that 2nd Re-screening Visit 1 has been scheduled.

Visit One Tasks	Notes
❑ Informed Consent	If applicable
❑ Electrophoresis	Does not have to be repeated unless subject has been transfused since the previous electrophoresis, and within 3 months of the re-screening visit.
❑ HIV Test	Need result within the last 12 months; may not need to re-test.
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Chemistry Panel[2]	
❑ Collect specimens for Central Labs	▪ Boston Lab (Brugnara): 3 vacutainers - 2 half-full 10-mL lavender; 1 full 5-mL green - If short on blood, these vacutainers should be filled first ▪ Duke Lab (Telen): 1 full 5-mL lavender vacutainer
❑ Prepare specimens for shipping	▪ Enter Specimen IDs into RhoLAB and affix labels to the RhoLAB Specimen ID Tracker. ▪ Place a copy of the RhoLAB Packing List in Subject Binder ▪ See the "Study Help Documents" tab for instructions.
❑ CRFs and EDC	▪ Inclusion Criteria, Exclusion Criteria ▪ Screening - requires % of hyperdense cells from RhoLAB e-mail ▪ Physical Exam ▪ Medical History, Health History – Update the Medical and Health History CRFs from Visit 1 to reflect any changes to the subject's medical history since the last time the subject was screened. ▪ Hematology Labs, Chemistry Labs ▪ Pregnancy Test As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

FOLLOWING VISIT: Confirm eligibility per e-mail from RhoLAB (% hyperdense) AND local lab values.

If Eligible:

- Save RhoLAB e-mail (% hyperdense cells) in Subject Binder
- Schedule Visit 2. Enter date of Visit 2 on Visit 1 2nd Re-Screening CRF, & e-mail date to CHAMPS_labs@rhoworld.com 7-10 days before Visit 2.

Screen Failures:

- Complete the Screen Failure Log CRF.

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CSCC
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Clinical Trials Consortium

CHAMPS Source Document Worksheet for Visit 1

This worksheet is also used for the
Re-screening Visit 1 and 2nd Re-screening Visit 1

Date: _____ / _____ / _____ **Visit #:** 1 **CSCC ID:** _____

Inclusion Criteria

Q5 – Does the subject exhibit regular adherence with comprehensive care? □ Yes □ No

Q6 – Is the subject in a steady state and not having an acute complication of SCD? □ Yes □ No

Exclusion Criteria

Q3 – In the investigator's opinion, has the subject exhibited poor adherence with previous treatment regimens? □ Yes □ No

Q8 – Has the subject had treatment with an investigational drug in the last 3 months? □ Yes □ No

Q9 – Does the subject have any other chronic illness other than SCD that might affect his/her responsiveness to study drug? □ Yes □ No

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Medical History

*Complete this section **only** if the information was provided by the subject and cannot be verified in the medical record. For Re-screening Visits, simply update the information collected at Visit 1.*

Has the subject ever had or ever been diagnosed with: (if selected, enter year of 1st diagnosis and if present/occurred in the last year)

	Year of 1st Dx	Last Year?
□ Acute Chest Syndrome		□
□ Avascular Necrosis of Hip(s)		□
□ Avascular Necrosis of Shoulder(s)		□
□ Stroke		□
□ CNS – Other, specify		□
□ CNS – Other, specify		□
□ Hypersplenism		□
□ Leg Ulcers		□
□ Priapism □ Not Applicable		□
□ Retinopathy		□
□ Acute Splenic Sequestration		□

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet for Visit 1

This worksheet is also used for the
Re-screening Visit 1 and 2nd Re-screening Visit 1

Health History

In the past 12 months, has the subject had any pain crisis(es) at home for which there was no hospitalization or ED/day hospital/urgent care visit? *Only record information not present in the medical record! For Re-screening Visits, simply update the information collected at Visit 1.*

□ Yes □ No

If yes, how many pain crises:

- Were treated at home? _____
- Were treated in a clinic or doctor's office, not hospital? _____

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

2nd Re-screening – Visit 1 (if applicable)

- Inclusion Criteria
- Exclusion Criteria
- Screening (Re-screen)
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Pregnancy Test
- Screen Failure Log for 2nd Re-screening – Visit 1

- **The Medical Health History CRF and the Health History CRF are not repeated here; please update the forms that were submitted with the original Visit 1 CRFs.**
- **If this subject has been re-screened AND been transfused within the last 3 months, please repeat the hemoglobin electrophoresis and enter the date of results and results in the Hemoglobinopathy section of the Visit 1 Screening CRF (page 3b of 11); this will replace the data that were previously entered.**

CRF COMPLETION GUIDELINES

Item	Instructions
Questions 3 and 6	Information obtained from *Health History* case report form (Visit 1, p. 7).
Note	Inclusion criterion #3 (Hb level 8-12.5 g/dL for children and adults), listed in the protocol, is incorporated into the CRF on the *Screening* page for this visit.

INCL

Comprehensive Sickle Cell Centers	**Inclusion Criteria**	**2nd Re-screening – Visit 1** Page: 1 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

For the subject to be eligible for this study, Questions 1 through 6 must be answered <u>Yes.</u>

1. Has the subject been diagnosed with Hb SC disease?	☐ Yes	☐ No
2. Is the subject 5 years of age or older?	☐ Yes	☐ No
3. Has the subject had at least one vaso-occlusive event (pain crisis[1], acute chest syndrome[2]) in the previous 12 months?	☐ Yes	☐ No
4. Has the subject/guardian signed an informed consent/assent form?	☐ Yes	☐ No
Date of informed consent: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)		
5. Does the subject exhibit regular adherence with comprehensive care?[3]	☐ Yes	☐ No
6. Is the subject in a steady state and not having an acute complication of sickle cell disease [i.e., no hospitalization, pain event, or episode of acute chest syndrome within the past month (30 days)]?	☐ Yes	☐ No

[1] A pain crisis is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours, requires a visit to a hospital, Emergency Department, clinic, or provider's office, and is not explained except by sickle cell disease.

[2] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[3] A subject has exhibited regular adherence when he/she has consistently shown up for scheduled clinic visits and when he/she has been scheduled for at least one clinic visit per year.

CRF COMPLETION GUIDELINES

Item	Instructions
Question 1	Information obtained from the medical record.
Questions 4 and 5	Information obtained from the medical record. Mark 'No' if no test was performed in the previous month.
Question 6	Information obtained from pregnancy test administered at entry for this visit. This question must be answered 'Yes' or 'No' for all subjects.
Question 7	Information obtained from medical record and subject interview. For the purposes of this study, "extended period of time" is defined as 6 months of daily use, per the subject's self-report.
Questions 2, 8 and 9	Information obtained from medical record and subject interview.
Note	Additional exclusion criteria are listed in the protocol. These criteria are incorporated into the CRF on the *Screening* page for this visit. These criteria are listed in the protocol as: • #10 < 3% RBC with density > 41 g/dL (as measured by Advia 120) • #11 positive HIV test.

EXCL

For the subject to be eligible for this study, Questions 1 through 9 must be answered No.

1. Has the subject had any previous treatment with hydroxyurea within the last 3 months? **Note: Subjects enrolled under Protocol Version 6.0 are excluded if EVER treated with hydroxyurea.**	☐ Yes	☐ No
2. Has the subject had any treatment with magnesium within the past 3 months (including vitamins containing magnesium)?	☐ Yes	☐ No
3. In the investigator's opinion, has the subject exhibited poor adherence with previous treatment regimens?	☐ Yes	☐ No
4. Has the subject had hepatic dysfunction (SGPT > 2x upper limit of normal) within the past month?	☐ Yes	☐ No
5. Has the subject had renal dysfunction (creatinine ≥ 1.0 mg/dL, < 18.0 years of age; ≥ 1.2 mg/dL, ≥ 18.0 years of age) within the past month?	☐ Yes	☐ No
6. Is the subject pregnant?	☐ Yes	☐ No
7. Has the subject had ≥ 10 hospital admissions (overnight stays) for pain in the last 12 months, or has he/she been using narcotics daily for an extended period of time? [1]	☐ Yes	☐ No
8. Has the subject had treatment with an investigational drug in last 3 months?	☐ Yes	☐ No
9. Does the subject have any other chronic illness or disorder other than SCD that could adversely affect the subject's performance in the study (e.g., tuberculosis)?	☐ Yes	☐ No

[1] For the purposes of this study, "extended period of time" is defined as 6 months of daily use, per the subject's self-report.

CRF COMPLETION GUIDELINES

Item	Instructions
Expected Date of Next Visit	In an effort to estimate the number of samples the Duke (Telen) Central Lab must prepare to analyze red blood cell adhesion, study coordinators are asked to provide the expected date of next visit and email it to CHAMPS_labs@rhoworld.com.
Red Cell Density	Information obtained from the e-mail sent to the site from Boston (Brugnara) Central Lab via RhoLAB. If the email is not received, study coordinators with RhoLAB access can log into the system and view the results for current subjects.
Hemoglobin Level	Information obtained from Hematology Labs case report form for this visit.
HIV Status	If the subject has not had an HIV test within the last 12 months, one must be performed before he/she can continue in this study.
Hepatic Dysfunction	Screening SGPT level obtained from *Chemistry Labs* case report form for this visit.
Renal Dysfunction	Screening creatinine level obtained from *Chemistry Labs* case report form for this visit.

SCRE

Comprehensive Sickle Cell Centers	**Screening (Re-screen)**	**2nd Re-screening – Visit 1** Page: 3a of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Expected Date of Next Visit: *(Within 1 - 3 weeks of Visit 1)* ☐☐ / ☐☐☐ / ☐☐ → *Email date to CHAMPS_labs@rhoworld.com*
Day Month Year

1) Red Cell Density:

% Hyperdense cells ☐☐.☐ % *% hyperdense cells will be provided via an e-mail from RhoLAB.*

If the subject has ≥ 3 percent RBCs with density > 41 g/dL, he/she is eligible to continue in this study.

2) Hemoglobin Level:

Does the subject have a Hb level between 8 – 12.5 g/dL? ☐ Yes ☐ No

If the subject has a Hb level between 8 – 12.5 g/dL, he/she is eligible to continue in this study.

3) Hb A %:

Has the subject been transfused within the past 3 months? ☐ Yes ☐ No

→ **If yes**, is the subject's Hb A ≤ 10%? ☐ Yes ☐ No

If the subject has a Hb A % ≤ 10, he/she is eligible to continue in this study.

4) HIV Status: (*tested within the last 12 months)*

Date tested: ☐☐ / ☐☐☐ / ☐☐ Result: ☐ Negative ☐ Positive
Day Month Year

If the subject has a negative HIV test, he/she is eligible to continue in this study.

5) Hepatic Dysfunction:

Within the past month, has the subject had SGPT > 2x the upper limit of normal? ☐ Yes ☐ No

Screening SGPT level (U/L) ☐☐☐☐ Local lab upper limit of normal (U/L) ☐☐☐☐

If the subject has not had SGPT > 2x upper limit of normal within the past month, he/she is eligible to continue in this study.

6) Renal Dysfunction:

Within the past month has subject had creatinine ≥ 1.0 mg/dL (if under age 18.0 years) or ≥ 1.2 mg/dL (if age 18.0 years or above)? ☐ Yes ☐ No

Screening creatinine level (mg/dL) ☐☐.☐ Local lab upper limit of normal (mg/dL) ☐☐.☐

If the subject has not had creatinine ≥ 1.0 mg/dL (if under age 18.0 years) or ≥ 1.2 mg/dL (if 18.0 years or above) within the past month, he/she is eligible to continue in this study.

Physical Exam

☐ Not Done → Specify_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*

(at the greatest distance below the left costal margin)

3) Does the subject have any skin lesions? ☐ Yes ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Is the subject taking any medication? ☐ Yes ☐ No

→ *If **yes**, record information on the Concomitant Medications CRF.*

→ *Be sure to check "Pre-existing" on the Concomitant Medications CRF.*

[1] Weight should be measured with the subject standing still, wearing light clothing (such as a paper exam gown), and no shoes.

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CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Hemoglobin	Hemoglobin must be between 8.0 and 12.5 g/dL at study entry. Use this value to answer the second question on the *Screening* CRF (Does the subject have an Hb level between 8.0 – 12.5 g/dL?)

HEMA

Comprehensive Sickle Cell Centers	**Hematology Labs**	**2nd Re-screening – Visit 1** Page: 5 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (/mm^3)	☐☐☐☐☐

→ Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	• For subjects < 18 years of age, creatinine must be ≤ 1.0 mg/dL. • For subjects ≥ 18, creatinine must be ≤ 1.2 mg/dL. • If this criteria is not met, the subject is not eligible to be in the study.
SGPT	• SGPT must be < 2x the upper limit of normal at study entry. • If this criteria is not met, the subject is not eligible to be in the study.

CHEM

Comprehensive Sickle Cell Centers	**Chemistry Labs**	**2nd Re-screening – Visit 1** Page: 6 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Sodium (mmol/L)	☐☐☐
Potassium (mmol/L)	☐.☐
Chloride (mmol/L)	☐☐☐
CO_2 (mmol/L)	☐☐.☐
BUN (mg/dL)	☐☐☐
Creatinine (mg/dL)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
SGPT/ALT (U/L)	☐☐☐☐
Alk phosphatase (U/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (g/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (U/L)	☐☐☐☐

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

PREG

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
General	This form should be completed the ***third time*** a subject discontinues prior to receiving study drug. The subject is no longer eligible for this study. If the subject discontinues prior to completing the 2nd Re-screening Visit, complete only this log. If the subject discontinues after completing the 2nd Re-screening Visit, complete this log and all 2nd Re-screening Visit forms.
Date of last contact	Record the date on which the subject was last contacted for a study related reason.
Primary reason subject not enrolled	Select the primary reason the subject was not enrolled. Specify if applicable.
Complete 2nd Re-screening Visit?	Check "Yes" or "No". If "No," provide the Date of Informed Consent. If "Yes," complete all CRFs for 2nd Re-screening Visit. Also update as appropriate, the two Medical History forms and the Health History form under the Visit 1 EDC link.

This form is to be completed the *third time* the subject discontinues prior to receiving study drug. The subject is no longer eligible for this study.

Date of last study related contact: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Primary Reason the subject will not be enrolled: (Check only one.)

- ☐ In the investigator's opinion, the subject's health, safety and/or well-being would be threatened by participation in the study.
- ☐ Subject lost to follow-up.
- ☐ Subject or subject's legal representative requested to withdraw. ***Specify:*** _____
- ☐ Subject did not meet inclusion/exclusion criteria.

  Is subject no longer in steady state after previously meeting inclusion/exclusion criteria? ☐ Yes ☐ No

  → **If Yes,** check all that apply and complete the Adverse Event forms.

  - ☐ Subject experienced one or more vaso-occlusive crises
  - ☐ Subject experienced one or more non-vaso-occlusive sickle events
  - ☐ Subject experienced one or more non-sickle related events

- ☐ Other Reason, ***Specify:*** _____

Did subject complete the 2nd Re-screening Visit? ☐ Yes ☐ No

→ **If no,** please provide the Date of Informed Consent at the 2nd Re-screening Visit. Also update as appropriate, the <u>two Medical History</u> forms and the <u>Health History</u> form under the Visit 1 EDC link.

Date of Informed Consent: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

→ **If yes,** be sure to complete all 2nd Re-screening CRFs.

Investigator's Statement:

I have reviewed the data entries within this CRF and, to the best of my knowledge, the data represent a complete and accurate record of the subject's participation in the study.

PI signature: _____ Signature Date: ☐☐ / ☐☐☐ / ☐☐☐☐ (Day / Month / Year)

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CHAMPS Study Checklist – Visit 2
(Baseline: Visit 1 + 1-3 Weeks)

Visit Two Tasks	Notes
❑ Randomize subject	File randomization e-mail in Subject Binder.
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration. Cancer and neuroimaging collected at Visits 1, 2, 7, 10, 13, and 16.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Chemistry Panel[2]	
❑ Urinalysis	
❑ Collect specimens for Central Labs	▪ Boston Lab (Brugnara): 3 vacutainers - 2 half-full 10-mL lavender; 1 full 5-mL green. If short on blood, these vacutainers should be filled first. ▪ Duke Lab (Telen): 1 full 5-mL lavender vacutainer
❑ Prepare specimens for shipping	▪ Enter Specimen IDs into RhoLAB and affix labels to the RhoLAB Specimen ID Tracker. ▪ Place a copy of the RhoLAB Packing List in Subject Binder.
❑ Study Drug	▪ Provide first dose of study drugs, dosing syringes and pill dispensers. ▪ Create and print Study Drug Log. On the first row, enter the first date that study drug will be taken; usually the day of (or day after) the visit. Remaining dates will autofill. ▪ Remind subjects that capsules should not be opened. ▪ Ask subject to bring Study Drug and Study Drug Log to next visit.
❑ Create a Study Visit Calendar	▪ Enter the dates of Visits 1 and 2; visit windows will autofill based on date of Visit 2. Ensure that dates are correct. The clock starts when the subject begins taking study drug. If there is a delay, enter that date as the date of Visit 2 on the Study Visit Calendar. ▪ File a copy of the Study Visit Calendar in the Subject Binder.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology and Chemistry Labs ▪ Pregnancy Test ▪ Urinalysis ▪ Study Drug Records and Study Drug Dosing Logs As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations
❑ Screen Failures	If subject is a screen failure, do not enter any visit 2 CRFs. Instead, complete the Visit 1 Screen Failure Log (Or the Re-Screening Screen Failure Log, as appropriate)

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

1 week after this visit:

☐ Call the subject with a reminder to bring study drug and the Study Drug Log to the next visit.

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

RhoLAB Specimen ID Tracker

January 4, 2007

Subject ID Number _____

Visit Date _____

10-mL lavender vacutainer

10-mL lavender vacutainer

5-mL green vacutainer

5-mL lavender vacutainer

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Visit Two

(Baseline 1-3 Weeks)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Urinalysis
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click "ADD" to enter data for each event that has occurred in the past year. • If a single event was treated in multiple locations, check the box corresponding to each location and provide all applicable dates. Do not click the 'ADD' button for each location. • Check all reasons that apply. Do not complete the specify field unless 'Other' is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as "reasons" may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject's self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject's self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter "yes" the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason "unknown" or "date part unknown" when prompted.

IHHX

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 2** Page: 1 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location: **Date of Encounter:**

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

All questions relate to events since the previous visit.

Cancer

Since Visit 1, has this subject been diagnosed with cancer? ☐ Yes ☐ No

→ **If yes,** record details below and complete Adverse Event and Serious Adverse Event forms as appropriate.

Date diagnosed: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type: _____

Location: _____

ADD

Neuroimaging

Since Visit 1, has this subject undergone any neuroimaging procedures? ☐ Yes ☐ No

→ **If yes,** click the ADD button and record details for each type of test.

→ Complete one record for each type of test.

Date of test: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type of test[1]: *(check one)* ☐ MRI ☐ MRA ☐ CT ☐ Cerebral angiography ☐ Other,specify _____

Was this result abnormal? ☐ Yes[2] ☐ No ☐ Equivocal[3]

If yes, describe brief findings: _____

_____

ADD

[1] Information about **"types of tests"** may be downloaded from the CHAMPS web page on the CSCC website.

[2] If **"result abnormal"** is **Yes** or **Equivocal**, fax results to the attention of CHAMPS at the SDMC (Rho, Inc.) 919-287-0126.

[3] If **"result abnormal"** is **Yes** or **Equivocal**, complete Adverse Event form.

Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.
Hemoglobin	The Hb level must be between 8.0 – 12.5 g/dL to be eligible for the study.

HEM2

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC ($x10^6/mm^3$)	☐.☐☐
WBC ($x10^3/mm^3$)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count ($x10^3/mm^3$)	☐☐☐☐
% Retic	☐☐.☐
OR	
ARC ($x10^3/mm^3$)	☐☐☐
ANC ($x10^3/mm^3$)	☐☐☐☐☐

→ Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.
Creatinine	• For subjects < 18 years of age, creatinine must be ≤ 1.0 mg/dL. • For subjects ≥ 18, creatinine must be ≤ 1.2 mg/dL.
SGPT	• SGPT must be < 2x the upper limit of normal at study entry.

CHE2

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Sodium (mmol/L)	☐☐☐
Potassium (mmol/L)	☐.☐
Chloride (mmol/L)	☐☐☐
CO_2 (mmol/L)	☐☐.☐
BUN (mg/dL)	☐☐☐
Creatinine (mg/dL)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
SGPT/ALT (U/L)	☐☐☐☐
Alk phosphatase (U/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (g/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (U/L)	☐☐☐☐

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

URIN

Comprehensive Sickle Cell Centers	**Urinalysis**	**Visit 2**
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ Labs not done
→Specify:_____

Protein *(Select one, as reported by your lab)*:

☐ Negative ☐ Trace ☐ 100 ☐ 200 ☐ 300 ☐ 1+ ☐ 2+ ☐ 3+

Microscopic RBC (#/mm^3):

☐ Negative ☐ 0-5 ☐ 5-10 ☐ 10-25 ☐ 25-50 ☐ 50+

Microscopic WBC (#/mm^3):

☐ Negative ☐ 0-5 ☐ 5-10 ☐ 10-25 ☐ 25-50 ☐ 50+

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

PREG

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

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Clinical Trials Consortium

CHAMPS Study Checklist – Visit 3
(Visit 2 ± 4 days)

Visit Three Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Study Drug	▪ Check Study Drug Log and count pills/check liquid. ▪ This is not a monthly visit, so a new supply of study drug is not dispensed. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

If this visit is also serving as a Toxicity Visit:

❑ Chemistry Panel[2]

❑ Chemistry Lab CRF

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

1 week after this visit:

□ Call the subject with a reminder to bring study drug and the Study Drug Log to the next visit.

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Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Visit Three

(Week 2 +/- 4 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for each event that has occurred in the past year. • If a single event was treated in multiple locations, check the box corresponding to each location and provide all applicable dates. Do not click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

IHHX

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 3** Page: 1a of 5
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location: **Date of Encounter:**

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

This page intentionally left blank.

Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\leq$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

HEM3

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 3** Page: 2 of 5
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
All Questions	Complete Chemistry Lab if this study visit is also serving as a Toxicity Visit. Subjects will be discontinued for hepatic dysfunction or renal toxicity only if either one is not resolved with dose reduction(s) in the study drug to which the toxicities are associated (HU or Mg). This decision will be made by the site's Principal Investigator (PI). If the site's PI is concerned with the increase in creatinine level or other evidence of renal toxicity, the site's PI should bring it to the attention of the study PI, who will work with the protocol team to determine the appropriate course of action.
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	Creatinine > 1.2 mg/dL for subjects < 18 years of age, or creatinine > 1.4 mg/dL for patients ≥ 18 is considered a toxicity and appropriate dose reduction procedures must be followed.
SGPT	If the SGPT value is ≥ 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

CHE3

Comprehensive Sickle Cell Centers	**Chemistry Labs**	**Visit 3** Page: 3 of 5
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Was a chemistry lab conducted for evaluation of toxicity?
→ **If yes**, complete this page.
→ **If no**, leave the remainder of the page blank.

☐ Yes ☐ No

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Creatinine (mg/dL)	☐☐.☐ ☐ Not required
SGPT/ALT (U/L)	☐☐☐☐ ☐ Not required

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

MGTX

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 3** Page: 4a of 5
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous visit.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

HYTX

All questions relate to events <u>since the previous visit</u>.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

PREG

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

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CHAMPS Study Checklist – Visit 4
(Week 4 ± 4 days)

Visit Four Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Study Drug	▪ Collect unused study drug and Study Drug Log ▪ Provide subject with a new supply of study drugs, dosing syringes/pill dispensers, and a Study Drug Log. ▪ Remind subjects that capsules should not be opened. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Records ▪ Study Drug Dosing Logs As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations
If the subject is transfused, electrophoresis is repeated as needed until the subject's Hb %A ≤ 10%.	

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

<u>If this visit is also serving as a Toxicity Visit:</u>

❑ Chemistry Panel[2]

❑ Chemistry Lab CRF

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

<u>1 week after this visit:</u>

□ Call the subject with a reminder to bring study drug and the Study Drug Log to the next visit.

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Visit Four

(Week 4 +/- 4 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 4** Page: 1 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location:

Date of Encounter:

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Hospital **Date Admitted:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) **Date Discharged:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

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Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\leq$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 4** Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
All Questions	Complete Chemistry Lab if this study visit is also serving as a Toxicity Visit. Subjects will be discontinued for hepatic dysfunction or renal toxicity only if either one is not resolved with dose reduction(s) in the study drug to which the toxicities are associated (HU or Mg). This decision will be made by the site's Principal Investigator (PI). If the site's PI is concerned with the increase in creatinine level or other evidence of renal toxicity, the site's PI should bring it to the attention of the study PI, who will work with the protocol team to determine the appropriate course of action.
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	Creatinine > 1.2 mg/dL for subjects < 18 years of age, or creatinine > 1.4 mg/dL for patients $\geq$ 18 is considered a toxicity and appropriate dose reduction procedures must be followed.
SGPT	If the SGPT value is $\geq$ 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

CHE3

Comprehensive Sickle Cell Centers	**Chemistry Labs**	**Visit 4** Page: 4 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Was a chemistry lab conducted for evaluation of toxicity?
→ **If yes**, complete this page.
→ **If no**, leave the remainder of the page blank.

☐ Yes ☐ No

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Creatinine (mg/dL)	☐☐.☐ ☐ Not required
SGPT/ALT (U/L)	☐☐☐☐ ☐ Not required

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 4** Page: 5a of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

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Clinical Trials Consortium

CHAMPS Study Checklist – Visit 5
(Week 6 ± 4 days)

Visit Five Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations
❑ Study Drug	▪ Check Study Drug Log and count pills/check liquid. ▪ This is not a monthly visit, so a new supply of study drug is not dispensed. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ E-mail estimated date of Visit 6 to CHAMPS_labs@rhoworld.com.	
❑ If the subject is transfused, electrophoresis is repeated as needed until the subject's Hb %A ≤ 10%. If not ≤ 10%, subject should come in for another test prior to Visit 6 for another electrophoresis.	

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

<u>If this visit is also serving as a Toxicity Visit:</u>

❑ Chemistry Panel[2]

❑ Chemistry Lab CRF

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

<u>1 week after this visit:</u>

□ Call the subject with a reminder to bring study drug and the Study Drug Log to the next visit.

The next study visit (Visit 6) is very important, as specimens collected will provide the data for the primary endpoint. Please ensure that this visit is scheduled within the visit window (Week 8 ± 4 days).

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Visit Five

(Week 6 +/- 4 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Expected Date of Next Visit	In an effort to estimate the number of samples the Duke (Telen) Central Lab must prepare to analyze red blood cell adhesion, study coordinators are asked to provide the expected date of next visit and email it to CHAMPS_labs@rhoworld.com.
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 5** Page: 1 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Expected Date of Next Visit: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) → *Email date to CHAMPS_labs@rhoworld.com*

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location: **Date of Encounter:**

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No **ADD**

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

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Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\underline{\leq}$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 5** Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
All Questions	Complete Chemistry Lab if this study visit is also serving as a Toxicity Visit. Subjects will be discontinued for hepatic dysfunction or renal toxicity only if either one is not resolved with dose reduction(s) in the study drug to which the toxicities are associated (HU or Mg). This decision will be made by the site's Principal Investigator (PI). If the site's PI is concerned with the increase in creatinine level or other evidence of renal toxicity, the site's PI should bring it to the attention of the study PI, who will work with the protocol team to determine the appropriate course of action.
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	Creatinine > 1.2 mg/dL for subjects < 18 years of age, or creatinine > 1.4 mg/dL for patients ≥ 18 is considered a toxicity and appropriate dose reduction procedures must be followed.
SGPT	If the SGPT value is ≥ 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

CHE3

Comprehensive Sickle Cell Centers	**Chemistry Labs**	**Visit 5** Page: 4 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Was a chemistry lab conducted for evaluation of toxicity?
→ **If yes**, complete this page.
→ **If no**, leave the remainder of the page blank.

☐ Yes ☐ No

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Creatinine (mg/dL)	☐☐.☐ ☐ Not required
SGPT/ALT (U/L)	☐☐☐☐ ☐ Not required

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 5** Page: 5a of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

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CHAMPS Study Checklist – Visit 6
(Week 8 ± 4 days)

Visit Six Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Chemistry Panel[2]	
❑ Collect specimens for Central Labs	▪ Boston Lab (Brugnara): 3 vacutainers - 2 half-full 10-mL lavender; 1 full 5-mL green. If short on blood, these vacutainers should be filled first. ▪ Duke Lab (Telen): 1 full 5-mL lavender vacutainer <u>Hold off on labs until the next visit IF subject has been:</u> ▪ transfused and Hb %A is currently >10%. ▪ off study drug for more than 3 days (toxicity, etc).
❑ Prepare specimens for shipping	▪ Enter Specimen IDs into RhoLAB and affix labels to the RhoLAB Specimen ID Tracker. ▪ Place a copy of the RhoLAB Packing List in Subject Binder
❑ Study Drug	▪ Collect unused study drug and Study Drug Log. ▪ Provide subject with a new supply of study drugs, dosing syringes/pill dispensers, and a Study Drug Log. ▪ Remind subjects that capsules should not be opened. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Records ▪ Study Drug Dosing Logs ▪ Chemistry Labs As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations
❑ Remind subject to bring unused study drug and Study Drug Log to Visit 7. Visits are now scheduled monthly, so this visit should take place in 4 weeks.	

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC
2) Sodium, Potassium, Chloride, CO2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

<u>FOLLOWING VISIT 6:</u> Follow-up call to subject 2 weeks after Visit 6, as study drug compliance may drop once visits are less frequent.

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CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

RhoLAB Specimen ID Tracker

January 4, 2007

Subject ID Number _____

Visit Date _____

10-mL lavender vacutainer

10-mL lavender vacutainer

5-mL green vacutainer

5-mL lavender vacutainer

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Visit Six

(Week 8 +/- 4 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 6** Page: 1 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location:

Date of Encounter:

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number)

Select one: ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

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Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\underline{\leq}$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 6** Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the “Labs Not Done” box and specify the reason the lab was not done.
Creatinine	Record lab results for each test using the units provided on the form: - For subjects < 18 years of age, creatinine must be ≤ 1.2 mg/dL. - For subjects ≥ 18, creatinine must be ≤ 1.4 mg/dL.
SGPT	SGPT must be < 2x the upper limit of normal.

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Sodium (mmol/L)	☐☐☐
Potassium (mmol/L)	☐.☐
Chloride (mmol/L)	☐☐☐
CO_2 (mmol/L)	☐☐.☐
BUN (mg/dL)	☐☐☐
Creatinine (mg/dL)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
SGPT/ALT (U/L)	☐☐☐☐
Alk phosphatase (U/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (g/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (U/L)	☐☐☐☐

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 6** Page: 5a of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

Comprehensive Sickle Cell Centers	**HU/Placebo Toxicity Check**	**Visit 6** Page: 5b of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

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CHAMPS Study Checklist – Visit 7
(Month 3 ± 8 days)

Visit Seven Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration. Cancer and neuroimaging collected at Visits 1, 2, 7, 10, 13, and 16.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Study Drug	▪ Collect unused study drug and Study Drug Log. ▪ Provide subject with a new supply of study drugs, dosing syringes/pill dispensers, and a Study Drug Log. ▪ Remind subjects that capsules should not be opened. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Records ▪ Study Drug Dosing Logs As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations
❑ E-mail estimated date of Visit 8 to CHAMPS_labs@rhoworld.com.	
❑ If the subject has been transfused, electrophoresis is repeated as needed until the subject's Hb %A ≤ 10%. If not ≤ 10%, subject should come in for another test prior to Visit 8 for another electrophoresis.	

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

<u>If this visit is also serving as a Toxicity Visit:</u>

❑ Chemistry Panel[2]

❑ Chemistry Lab CRF

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

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Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Visit Seven

(Month 3 +/- 8 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Expected Date of Next Visit	In an effort to estimate the number of samples the Duke (Telen) Central Lab must prepare to analyze red blood cell adhesion, study coordinators are asked to provide the expected date of next visit and email it to CHAMPS_labs@rhoworld.com.
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 7** Page: 1 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Expected Date of Next Visit: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) → *Email date to CHAMPS_labs@rhoworld.com*

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location: **Date of Encounter:**

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

All questions relate to events since Visit 2.

Cancer

Since Visit 2, has this subject been diagnosed with cancer? ☐ Yes ☐ No

→ **If yes,** record details below and complete Adverse Event and Serious Adverse Event forms as appropriate.

Date diagnosed: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type: _____

Location: _____

ADD

Neuroimaging

Since Visit 2, has this subject undergone any neuroimaging procedures? ☐ Yes ☐ No

→ **If yes,** click the ADD button and record details for each type of test.

→ Complete one record for each type of test.

Date of test[1]: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type of test: *(check one)* ☐ MRI ☐ MRA ☐ CT ☐ Cerebral angiography ☐ Other,specify _____

Was this result abnormal? ☐ Yes[2] ☐ No ☐ Equivocal[3]

If yes, describe brief findings: _____

_____

ADD

[1] Information about **"types of tests"** may be downloaded from the CHAMPS web page on the CSCC website.

[2] **If "result abnormal" is Yes or Equivocal**, fax results to the attention of CHAMPS at the SDMC (Rho, Inc.) 919-287-0126.

[3] **If "result abnormal" is Yes or Equivocal**, complete Adverse Event form.

Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\leq$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 7** Page: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
All Questions	Complete Chemistry Lab if this study visit is also serving as a Toxicity Visit. Subjects will be discontinued for hepatic dysfunction or renal toxicity only if either one is not resolved with dose reduction(s) in the study drug to which the toxicities are associated (HU or Mg). This decision will be made by the site's Principal Investigator (PI). If the site's PI is concerned with the increase in creatinine level or other evidence of renal toxicity, the site's PI should bring it to the attention of the study PI, who will work with the protocol team to determine the appropriate course of action.
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	Creatinine > 1.2 mg/dL for subjects < 18 years of age, or creatinine > 1.4 mg/dL for patients $\geq$ 18 is considered a toxicity and appropriate dose reduction procedures must be followed.
SGPT	If the SGPT value is $\geq$ 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

Comprehensive Sickle Cell Centers	**Chemistry Labs**	**Visit 7** Page: 5 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Was a chemistry lab conducted for evaluation of toxicity?
→ **If yes**, complete this page.
→ **If no**, leave the remainder of the page blank.

☐ Yes ☐ No

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Creatinine (mg/dL)	☐☐.☐ ☐ Not required
SGPT/ALT (U/L)	☐☐☐☐ ☐ Not required

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 7** Page: 6a of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Study Checklist – Visit 8
(Month 4 ± 8 days)

Visit Eight Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Chemistry Panel[2]	
❑ Collect specimens for Central Labs	▪ Boston Lab (Brugnara): 3 vacutainers - 2 half-full 10-mL lavender; 1 full 5-mL green. If short on blood, these vacutainers should be filled first. ▪ Duke Lab (Telen): 1 full 5-mL lavender vacutainer <u>Hold off on labs until the next visit IF subject has been:</u> ▪ transfused and Hb %A is currently >10%. ▪ off study drug for more than 3 days (toxicity, etc).
❑ Prepare specimens for shipping	▪ Enter Specimen IDs into RhoLAB and affix labels to the RhoLAB Specimen ID Tracker. ▪ Place a copy of the RhoLAB Packing List in Subject Binder
❑ Study Drug	▪ Collect unused study drug and Study Drug Log. ▪ Provide subject with a new supply of study drugs, dosing syringes/pill dispensers, and a Study Drug Log. ▪ Remind subjects that capsules should not be opened. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Records ▪ Study Drug Dosing Logs ▪ Chemistry Labs As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC
2) Sodium, Potassium, Chloride, CO2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

RhoLAB Specimen ID Tracker

January 4, 2007

Subject ID Number _____

Visit Date _____

10-mL lavender vacutainer

10-mL lavender vacutainer

5-mL green vacutainer

5-mL lavender vacutainer

This page intentionally left blank.

Visit Eight

(Month 4 +/- 8 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 8** Page: 1 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location:

Date of Encounter:

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number)

Select one: ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

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Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\leq$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 8** Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the “Labs Not Done” box and specify the reason the lab was not done.
Creatinine	Record lab results for each test using the units provided on the form: - For subjects < 18 years of age, creatinine must be ≤ 1.2 mg/dL. - For subjects ≥ 18, creatinine must be ≤ 1.4 mg/dL.
SGPT	SGPT must be < 2x the upper limit of normal.

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Sodium (mmol/L)	☐☐☐
Potassium (mmol/L)	☐.☐
Chloride (mmol/L)	☐☐☐
CO_2 (mmol/L)	☐☐.☐
BUN (mg/dL)	☐☐☐
Creatinine (mg/dL)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
SGPT/ALT (U/L)	☐☐☐☐
Alk phosphatase (U/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (g/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (U/L)	☐☐☐☐

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 8** Page: 5a of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

Comprehensive Sickle Cell Centers	**HU/Placebo Toxicity Check**	**Visit 8** Page: 5b of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

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Clinical Trials Consortium

CHAMPS Study Checklist – Visit 9
(Month 5 ± 8 days)

Visit Nine Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Study Drug	▪ Collect unused study drug and Study Drug Log. ▪ Provide subject with a new supply of study drugs, dosing syringes/pill dispensers, and a Study Drug Log. ▪ Remind subjects that capsules should not be opened. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Records ▪ Study Drug Dosing Logs As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations
❑ E-mail estimated date of Visit 10 to CHAMPS_labs@rhoworld.com.	
❑ If the subject is transfused, electrophoresis is repeated as needed until the subject's Hb %A ≤ 10%. If not ≤ 10%, subject should come in for another test prior to Visit 10 for another electrophoresis.	

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

<u>If this visit is also serving as a Toxicity Visit:</u>

- ❑ Chemistry Panel[2]
- ❑ Chemistry Lab CRF

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

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CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Visit Nine

(Month 5 +/- 8 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Expected Date of Next Visit	In an effort to estimate the number of samples the Duke (Telen) Central Lab must prepare to analyze red blood cell adhesion, study coordinators are asked to provide the expected date of next visit and email it to CHAMPS_labs@rhoworld.com.
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 9** Page: 1 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location:

Date of Encounter:

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

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Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*

(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\underline{\leq}$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 9** Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
All Questions	Complete Chemistry Lab if this study visit is also serving as a Toxicity Visit. Subjects will be discontinued for hepatic dysfunction or renal toxicity only if either one is not resolved with dose reduction(s) in the study drug to which the toxicities are associated (HU or Mg). This decision will be made by the site's Principal Investigator (PI). If the site's PI is concerned with the increase in creatinine level or other evidence of renal toxicity, the site's PI should bring it to the attention of the study PI, who will work with the protocol team to determine the appropriate course of action.
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	Creatinine > 1.2 mg/dL for subjects < 18 years of age, or creatinine > 1.4 mg/dL for patients $\geq$ 18 is considered a toxicity and appropriate dose reduction procedures must be followed.
SGPT	If the SGPT value is $\geq$ 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

Comprehensive Sickle Cell Centers	**Chemistry Labs**	**Visit 9** Page: 4 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Was a chemistry lab conducted for evaluation of toxicity?
→ **If yes**, complete this page.
→ **If no**, leave the remainder of the page blank.

☐ Yes ☐ No

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE	
Creatinine (mg/dL)	☐☐.☐	☐ Not required
SGPT/ALT (U/L)	☐☐☐☐	☐ Not required

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 9** Page: 5a of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

Comprehensive Sickle Cell Centers	**HU/Placebo Toxicity Check**	**Visit 9** Page: 5b of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

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CHAMPS Study Checklist – Visit 10
(Month 6 ± 8 days)

Visit Ten Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration. Cancer and neuroimaging collected at Visits 1, 2, 7, 10, 13, and 16.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Chemistry Panel[2]	
❑ Urinalysis	
❑ Collect specimens for Central Labs	▪ Boston Lab (Brugnara): 3 vacutainers - 2 half-full 10-mL lavender; 1 full 5-mL green - If short on blood, these vacutainers should be filled first ▪ Duke Lab (Telen): 1 full 5-mL lavender vacutainer <u>Hold off on labs until the next visit IF subject has been:</u> ▪ transfused and Hb %A is currently >10%. ▪ off study drug for more than 3 days (toxicity, etc).
❑ Prepare specimens for shipping	▪ Enter Specimen IDs into RhoLAB and affix labels to the RhoLAB Specimen ID Tracker. ▪ Place a copy of the RhoLAB Packing List in Subject Binder.
❑ Study Drug	▪ Collect unused study drug and Study Drug Log. ▪ Provide subject with a new supply of study drugs, dosing syringes/pill dispensers, and a Study Drug Log. ▪ Remind subjects that capsules should not be opened. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Records ▪ Study Drug Dosing Logs ▪ Chemistry Labs ▪ Urinalysis As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

2) Sodium, Potassium, Chloride, CO2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

CSCC
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Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

RhoLAB Specimen ID Tracker

January 4, 2007

Subject ID Number _____

Visit Date _____

10-mL lavender vacutainer

10-mL lavender vacutainer

5-mL green vacutainer

5-mL lavender vacutainer

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Visit Ten

(Month 6 +/- 8 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Urinalysis
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 10** Page: 1 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location: **Date of Encounter:**

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Hospital **Date Admitted:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) **Date Discharged:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

All questions relate to events since Visit 7.

Cancer

Since Visit 7, has this subject been diagnosed with cancer? ☐ Yes ☐ No

→ **If yes,** record details below and complete Adverse Event and Serious Adverse Event forms as appropriate.

Date diagnosed: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type: _____

Location: _____

ADD

Neuroimaging

Since Visit 7, has this subject undergone any neuroimaging procedures? ☐ Yes ☐ No

→ **If yes,** click the ADD button and record details for each type of test.

→ Complete one record for each type of test.

Date of test: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type of test[1]: *(check one)* ☐ MRI ☐ MRA ☐ CT ☐ Cerebral angiography ☐ Other,specify _____

Was this result abnormal? ☐ Yes[2] ☐ No ☐ Equivocal[3]

If yes, describe brief findings: _____

_____

ADD

[1] Information about **"types of tests"** may be downloaded from the CHAMPS web page on the CSCC website.

[2] **If "result abnormal" is Yes or Equivocal**, fax results to the attention of CHAMPS at the SDMC (Rho, Inc.) 919-287-0126.

[3] **If "result abnormal" is Yes or Equivocal**, complete Adverse Event form.

Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\underline{\leq}$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 10** Page: 4 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the “Labs Not Done” box and specify the reason the lab was not done.
Creatinine	Record lab results for each test using the units provided on the form: - For subjects < 18 years of age, creatinine must be ≤ 1.2 mg/dL. - For subjects ≥ 18, creatinine must be ≤ 1.4 mg/dL.
SGPT	SGPT must be < 2x the upper limit of normal.

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Sodium (mmol/L)	☐☐☐
Potassium (mmol/L)	☐.☐
Chloride (mmol/L)	☐☐☐
CO_2 (mmol/L)	☐☐.☐
BUN (mg/dL)	☐☐☐
Creatinine (mg/dL)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
SGPT/ALT (U/L)	☐☐☐☐
Alk phosphatase (U/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (g/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (U/L)	☐☐☐☐

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 10** Page: 6a of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

***Collection Date:** ☐☐/☐☐☐/☐☐ (Day / Month / Year)

☐ Labs not done
→Specify:_____

Protein *(Select one, as reported by your lab)*:

☐ Negative ☐ Trace ☐ 100 ☐ 200 ☐ 300 ☐ 1+ ☐ 2+ ☐ 3+

Microscopic RBC (#/mm^3):

☐ Negative ☐ 0-5 ☐ 5-10 ☐ 10-25 ☐ 25-50 ☐ 50+

Microscopic WBC (#/mm^3):

☐ Negative ☐ 0-5 ☐ 5-10 ☐ 10-25 ☐ 25-50 ☐ 50+

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Study Checklist – Visit 11
(Month 7 ± 8 days)

Visit Eleven Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Study Drug	▪ Collect unused study drug and Study Drug Log. ▪ Provide subject with a new supply of study drugs, dosing syringes/pill dispensers, and a Study Drug Log. ▪ Remind subjects that capsules should not be opened. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Records ▪ Study Drug Dosing Logs As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

<u>If this visit is also serving as a Toxicity Visit:</u>

- ❑ Chemistry Panel[2]
- ❑ Chemistry Lab CRF

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Visit Eleven

(Month 7 +/- 8 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 11**
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location: **Date of Encounter:**

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

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Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\underline{\leq}$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 11** Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
All Questions	Complete Chemistry Lab if this study visit is also serving as a Toxicity Visit. Subjects will be discontinued for hepatic dysfunction or renal toxicity only if either one is not resolved with dose reduction(s) in the study drug to which the toxicities are associated (HU or Mg). This decision will be made by the site's Principal Investigator (PI). If the site's PI is concerned with the increase in creatinine level or other evidence of renal toxicity, the site's PI should bring it to the attention of the study PI, who will work with the protocol team to determine the appropriate course of action.
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	Creatinine > 1.2 mg/dL for subjects < 18 years of age, or creatinine > 1.4 mg/dL for patients $\geq$ 18 is considered a toxicity and appropriate dose reduction procedures must be followed.
SGPT	If the SGPT value is $\geq$ 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

Comprehensive Sickle Cell Centers	**Chemistry Labs**	**Visit 11**
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Was a chemistry lab conducted for evaluation of toxicity?
→ **If yes**, complete this page.
→ **If no**, leave the remainder of the page blank.

☐ Yes ☐ No

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Creatinine (mg/dL)	☐☐.☐ ☐ Not required
SGPT/ALT (U/L)	☐☐☐☐ ☐ Not required

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 11** Page: 5a of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

All questions relate to events <u>since the previous visit</u>.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

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CHAMPS Study Checklist – Visit 12
(Month 8 ± 8 days)

Visit Twelve Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Chemistry Panel[2]	
❑ Study Drug	▪ Collect unused study drug and Study Drug Log. ▪ Provide subject with a new supply of study drugs, dosing syringes/pill dispensers, and a Study Drug Log. ▪ Remind subjects that capsules should not be opened. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Records ▪ Study Drug Dosing Logs ▪ Chemistry Labs As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC
2) Sodium, Potassium, Chloride, CO2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

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CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Visit Twelve

(Month 8 +/- 8 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 12** Page: 1 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location:

Date of Encounter:

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No **ADD**

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

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Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\leq$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 12** Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the “Labs Not Done” box and specify the reason the lab was not done.
Creatinine	Record lab results for each test using the units provided on the form: - For subjects < 18 years of age, creatinine must be ≤ 1.2 mg/dL. - For subjects ≥ 18, creatinine must be ≤ 1.4 mg/dL.
SGPT	SGPT must be < 2x the upper limit of normal.

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Sodium (mmol/L)	☐☐☐
Potassium (mmol/L)	☐.☐
Chloride (mmol/L)	☐☐☐
CO_2 (mmol/L)	☐☐.☐
BUN (mg/dL)	☐☐☐
Creatinine (mg/dL)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
SGPT/ALT (U/L)	☐☐☐☐
Alk phosphatase (U/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (g/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (U/L)	☐☐☐☐

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 12** Page: 5a of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Study Checklist – Visit 13
(Month 9 ± 8 days)

Visit Thirteen Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration. Cancer and neuroimaging collected at Visits 1, 2, 7, 10, 13, and 16.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Study Drug	▪ Collect unused study drug and Study Drug Log. ▪ Provide subject with a new supply of study drugs, dosing syringes/pill dispensers, and a Study Drug Log. ▪ Remind subjects that capsules should not be opened. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Records ▪ Study Drug Dosing Logs As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

<u>If this visit is also serving as a Toxicity Visit:</u>

- ❑ Chemistry Panel[2]
- ❑ Chemistry Lab CRF

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

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CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Visit Thirteen

(Month 9 +/- 8 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 13** Page: 1 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location:

Date of Encounter:

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

All questions relate to events since Visit 10.

Cancer

Since Visit 10, has this subject been diagnosed with cancer? ☐ Yes ☐ No

→ **If yes,** record details below and complete Adverse Event and Serious Adverse Event forms as appropriate.

Date diagnosed: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type: _____

Location: _____

ADD

Neuroimaging

Since Visit 10, has this subject undergone any neuroimaging procedures? ☐ Yes ☐ No

→ **If yes,** click the ADD button and record details for each type of test.

→ Complete one record for each type of test.

Date of test: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type of test[1]: *(check one)* ☐ MRI ☐ MRA ☐ CT ☐ Cerebral angiography ☐ Other,specify _____

Was this result abnormal? ☐ Yes[2] ☐ No ☐ Equivocal[3]

If yes, describe brief findings: _____

_____

ADD

[1] Information about **"types of tests"** may be downloaded from the CHAMPS web page on the CSCC website.

[2] **If "result abnormal" is Yes or Equivocal**, fax results to the attention of CHAMPS at the SDMC (Rho, Inc.) 919-287-0126.

[3] **If "result abnormal" is Yes or Equivocal**, complete Adverse Event form.

Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\leq$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 13** Page: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
All Questions	Complete Chemistry Lab if this study visit is also serving as a Toxicity Visit. Subjects will be discontinued for hepatic dysfunction or renal toxicity only if either one is not resolved with dose reduction(s) in the study drug to which the toxicities are associated (HU or Mg). This decision will be made by the site's Principal Investigator (PI). If the site's PI is concerned with the increase in creatinine level or other evidence of renal toxicity, the site's PI should bring it to the attention of the study PI, who will work with the protocol team to determine the appropriate course of action.
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	Creatinine > 1.2 mg/dL for subjects < 18 years of age, or creatinine > 1.4 mg/dL for patients $\geq$ 18 is considered a toxicity and appropriate dose reduction procedures must be followed.
SGPT	If the SGPT value is $\geq$ 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

Comprehensive Sickle Cell Centers	**Chemistry Labs**	**Visit 13** Page: 5 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Was a chemistry lab conducted for evaluation of toxicity?
→ **If yes**, complete this page.
→ **If no**, leave the remainder of the page blank.

☐ Yes ☐ No

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE	
Creatinine (mg/dL)	☐☐.☐	☐ Not required
SGPT/ALT (U/L)	☐☐☐☐	☐ Not required

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 13** Page: 6a of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

Comprehensive Sickle Cell Centers	**HU/Placebo Toxicity Check**	**Visit 13** Page: 6b of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Study Checklist – Visit 14
(Month 10 ± 8 days)

Visit Fourteen Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Chemistry Panel[2]	
❑ Study Drug	▪ Collect unused study drug and Study Drug Log. ▪ Provide subject with a new supply of study drugs, dosing syringes/pill dispensers, and a Study Drug Log. ▪ Remind subjects that capsules should not be opened. ▪ Ask subject to bring study drug and Study Drug Log to next visit.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Records ▪ Study Drug Dosing Logs ▪ Chemistry Labs As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations
❑ E-mail estimated date of Visit 15 to CHAMPS_labs@rhoworld.com	
❑ If the subject is transfused, electrophoresis is repeated as needed until the subject's Hb %A ≤ 10%. If not ≤ 10%, subject should come in for another test prior to Visit 15 for another electrophoresis.	

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC
2) Sodium, Potassium, Chloride, CO2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

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CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

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Visit Fourteen

(Month 10 +/- 8 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Expected Date of Next Visit	In an effort to estimate the number of samples the Duke (Telen) Central Lab must prepare to analyze red blood cell adhesion, study coordinators are asked to provide the expected date of next visit and email it to CHAMPS_labs@rhoworld.com.
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 14** Page: 1 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Expected Date of Next Visit: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) → *Email date to CHAMPS_labs@rhoworld.com*

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location: **Date of Encounter:**

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No **ADD**

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

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Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\leq$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Visit 14** Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the “Labs Not Done” box and specify the reason the lab was not done.
Creatinine	Record lab results for each test using the units provided on the form: - For subjects < 18 years of age, creatinine must be ≤ 1.2 mg/dL. - For subjects ≥ 18, creatinine must be ≤ 1.4 mg/dL.
SGPT	SGPT must be < 2x the upper limit of normal.

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Sodium (mmol/L)	☐☐☐
Potassium (mmol/L)	☐.☐
Chloride (mmol/L)	☐☐☐
CO_2 (mmol/L)	☐☐.☐
BUN (mg/dL)	☐☐☐
Creatinine (mg/dL)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
SGPT/ALT (U/L)	☐☐☐☐
Alk phosphatase (U/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (g/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (U/L)	☐☐☐☐

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 14** Page: 5a of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

All questions relate to events <u>since the previous visit</u>.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

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Clinical Trials Consortium

CHAMPS Study Checklist – Visit 15
(Month 11 ± 8 days)

Visit Fifteen Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration.
❑ Hematology Panel (CBC)[1]	
❑ Pregnancy Test	
❑ Study Drug	▪ Collect unused study drug and Study Drug Log. ▪ No study drug is dispensed at this visit.
❑ Collect specimens for Central Labs	▪ Boston Lab (Brugnara): 3 vacutainers - 2 half-full 10-mL lavender; 1 full 5-mL green - If short on blood, these vacutainers should be filled first ▪ Duke Lab (Telen): 1 full 5-mL lavender vacutainer <u>Hold off on labs until the next visit IF subject has been:</u> ▪ transfused and Hb %A is currently >10%. ▪ off study drug for more than 3 days (toxicity, etc).
❑ Prepare specimens for shipping	▪ Enter Specimen IDs into RhoLAB and affix labels to the RhoLAB Specimen ID Tracker. ▪ Place a copy of the RhoLAB Packing List in Subject Binder ▪ CSCC ID # required for data entry into RhoLAB. ▪ See the "Study Help Documents" tab for instructions.
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Pregnancy Test ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Records ▪ Study Drug Dosing Logs As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC

<u>If this visit is also serving as a Toxicity Visit:</u>

- ❑ Chemistry Panel[2]
- ❑ Chemistry Lab CRF

2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

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Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

RhoLAB Specimen ID Tracker

January 4, 2007

Subject ID Number _____

Visit Date _____

10-mL lavender vacutainer

10-mL lavender vacutainer

5-mL green vacutainer

5-mL lavender vacutainer

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Visit Fifteen

(Month 11 +/- 8 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Pregnancy Test

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 15** Page: 1 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location:

Date of Encounter:

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Hospital **Date Admitted:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) **Date Discharged:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

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Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\underline{\leq}$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ / ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
All Questions	Complete Chemistry Lab if this study visit is also serving as a Toxicity Visit. Subjects will be discontinued for hepatic dysfunction or renal toxicity only if either one is not resolved with dose reduction(s) in the study drug to which the toxicities are associated (HU or Mg). This decision will be made by the site's Principal Investigator (PI). If the site's PI is concerned with the increase in creatinine level or other evidence of renal toxicity, the site's PI should bring it to the attention of the study PI, who will work with the protocol team to determine the appropriate course of action.
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	Creatinine > 1.2 mg/dL for subjects < 18 years of age, or creatinine > 1.4 mg/dL for patients $\geq$ 18 is considered a toxicity and appropriate dose reduction procedures must be followed.
SGPT	If the SGPT value is $\geq$ 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

Comprehensive Sickle Cell Centers	**Chemistry Labs**	**Visit 15** Page: 4 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Was a chemistry lab conducted for evaluation of toxicity?
→ **If yes**, complete this page.
→ **If no**, leave the remainder of the page blank.

☐ Yes ☐ No

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Creatinine (mg/dL)	☐☐.☐ ☐ Not required
SGPT/ALT (U/L)	☐☐☐☐ ☐ Not required

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 presents life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 15** Page: 5a of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.

Pregnancy Test

☐ Not Done *(Check reason below)*

- ☐ Subject male
- ☐ Subject has not reached menstruating age
- ☐ Postmenopausal
- ☐ Hysterectomy
- ☐ Tubal ligation
- ☐ Other, specify:

_____

*Date of Collection: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Type: ☐ Serum ☐ Urine

Result: ☐ Positive ☐ Negative

* If the collection date differs from the visit date for this visit, explain: _____.

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Study Checklist – Visit 16
(Month 12 ± 8 days)

Prior to visit: Review Study Completion CRF and guidelines.

Visit Sixteen Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration.
❑ Hematology Panel (CBC)[1]	
❑ Chemistry Panel[2]	
❑ Urinalysis	
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Urinalysis ▪ Chemistry Labs ▪ Study Completion Form As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations
❑ Ask Subject and/or parent if he/she has a guess into which arm he/she was randomized, and whether or not he/she would like to remain on study drug. Record on the Study Completion CRF.	
❑ This is the last study visit. Remember that AEs should be followed until resolved.	

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC
2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

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Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Visit Sixteen

(Month 12 +/- 8 days)

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Urinalysis

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Visit 16** Page: 1 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location: **Date of Encounter:**

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

All questions relate to events since Visit 13.

Cancer

Since Visit 13, has this subject been diagnosed with cancer? ☐ Yes ☐ No

→ **If yes,** record details below and complete Adverse Event and Serious Adverse Event forms as appropriate.

Date diagnosed: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type: _____

Location: _____

ADD

Neuroimaging

Since Visit 13, has this subject undergone any neuroimaging procedures? ☐ Yes ☐ No

→ **If yes,** click the ADD button and record details for each test/type.

Date of test: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type of test[1]: *(check one)* ☐ MRI ☐ MRA ☐ CT ☐ Cerebral angiography ☐ Other,specify _____

Was this result abnormal? ☐ Yes[2] ☐ No ☐ Equivocal[3]

If yes, describe brief findings: _____

_____

ADD

[1] Information about **"types of tests"** may be downloaded from the CHAMPS web page on the CSCC website.

[2] **If "result abnormal" is Yes or Equivocal**, fax results to the attention of CHAMPS at the SDMC (Rho, Inc.) 919-287-0126.

[3] **If "result abnormal" is Yes or Equivocal**, complete Adverse Event form.

Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\leq$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ / ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the “Labs Not Done” box and specify the reason the lab was not done.
Creatinine	Record lab results for each test using the units provided on the form: - For subjects < 18 years of age, creatinine must be ≤ 1.2 mg/dL. - For subjects ≥ 18, creatinine must be ≤ 1.4 mg/dL.
SGPT	SGPT must be < 2x the upper limit of normal.

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Sodium (mmol/L)	☐☐☐
Potassium (mmol/L)	☐.☐
Chloride (mmol/L)	☐☐☐
CO_2 (mmol/L)	☐☐.☐
BUN (mg/dL)	☐☐☐
Creatinine (mg/dL)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
SGPT/ALT (U/L)	☐☐☐☐
Alk phosphatase (U/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (g/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (U/L)	☐☐☐☐

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 is life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Visit 16** Page: 6a of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

Comprehensive Sickle Cell Centers	**HU/Placebo Toxicity Check**	**Visit 16** Page: 6b of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Comprehensive Sickle Cell Centers	**Urinalysis**	**Visit 16**
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ Labs not done
→Specify:_____

Protein *(Select one, as reported by your lab)*:

☐ Negative ☐ Trace ☐ 100 ☐ 200 ☐ 300 ☐ 1+ ☐ 2+ ☐ 3+

Microscopic RBC (#/mm^3):

☐ Negative ☐ 0-5 ☐ 5-10 ☐ 10-25 ☐ 25-50 ☐ 50+

Microscopic WBC (#/mm^3):

☐ Negative ☐ 0-5 ☐ 5-10 ☐ 10-25 ☐ 25-50 ☐ 50+

* If the collection date differs from the visit date for this visit, explain: _____.

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Study Checklist – Early Termination
(30 days ± 8 from the previous study visit)

Subjects who withdraw early after taking study drug are asked to return in 30 days for a safety follow-up. Prior to visit: Review Study Completion CRF and guidelines.

Early Termination Tasks	Notes
❑ Clinical Evaluations	Brief physical exam to ensure general health
❑ Clinical Outcomes	Pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration.
❑ Hematology Panel (CBC)[1]	
❑ Chemistry Panel[2]	
❑ Urinalysis	
❑ CRFs and EDC	▪ Physical Exam ▪ Interim Health History ▪ Hematology Labs ▪ Toxicity Check – if subject experiences toxicity, he/she should return in 1 week for a Toxicity Visit ▪ Study Drug Record ▪ Study Drug Administration Log ▪ Urinalysis ▪ Chemistry Labs ▪ Study Completion Form As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations
❑ Ask Subject and/or parent if he/she has a guess into which arm he/she was randomized, and whether or not he/she would like to remain on study drug. Record on the Study Completion CRF.	
❑ This is the last study visit. Remember that AEs should be followed until resolved.	

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC
2) Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

If the subject withdraws ***after*** completing Visit 6, please collect Central Labs ***only if*** not collected at the previous visit.

❑ Collect specimens for Central Labs	▪ Boston Lab (Brugnara): 3 vacutainers - 2 half-full 10-mL lavender; 1 full 5-mL green - If short on blood, these vacutainers should be filled first ▪ Duke Lab (Telen): 1 full 5-mL lavender vacutainer
❑ Prepare specimens for shipping	▪ Enter Specimen IDs into RhoLAB and affix labels to the RhoLAB Specimen ID Tracker. ▪ Place a copy of the RhoLAB Packing List in Subject Binder. ▪ CSCC ID # required for data entry into RhoLAB. ▪ See the "Study Help Documents" tab for instructions.

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet
Visits 2-16 and Early Termination Visit

Date: _____ / _____ / _____ **Visit #: _____** **CSCC ID: _____**

Physical Exam:

Weight _____ kg

Is the spleen palpable? □ Yes □ No If yes, what is the current spleen size? ____ cm

Does the subject have any skin lesions? □ Yes □ No If yes, where are the lesions located? _____

Is the subject taking any medication? List…

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

RhoLAB Specimen ID Tracker

January 4, 2007

Subject ID Number _____

Visit Date _____

10-mL lavender vacutainer

10-mL lavender vacutainer

5-mL green vacutainer

5-mL lavender vacutainer

Early Termination

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Urinalysis

CRF COMPLETION GUIDELINES

Item	Instructions
Acute Events Leading to Hospitalization, Emergency Department, or Clinic Visit	• Click “ADD” to enter data for <u>each event</u> that has occurred in the past year. • If a <u>single event</u> was treated in <u>multiple locations</u>, check the box corresponding to each location and provide all applicable dates. <u>Do not</u> click the ‘ADD’ button for each location. • Check all reasons that apply. Do not complete the specify field unless ‘Other’ is marked and another reason not present in the list of reasons is specified. Use the comments field at the bottom of the page if more information about a reason that is already present in the list needs to be supplied. • Definitions for acute events listed as “reasons” may be downloaded from the CHAMPS page on the CSCC website.
Pain Crises	Information regarding treatment at home to be determined by subject’s self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject’s self-report. **Any information determined by subject self-report must be added to the medical record.**
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter “yes” the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason “unknown” or “date part unknown” when prompted.

Comprehensive Sickle Cell Centers	**Interim Health History**	**Early Termination**
Hydroxyurea & Magnesium Pidolate (CHAMPS)	**Date of Visit:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events since the previous study visit.

1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency department/day hospital/urgent care facility, or a hospitalization? ☐ Yes ☐ No

→**If yes,** click the "ADD" button and record information for each event

Treatment Location: **Date of Encounter:**

☐ Physician's Office / Clinic ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ Emergency Department / Day Hospital / Urgent Care ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date Admitted: **Date Discharged:**

☐ Hospital ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason(s)[1]:

☐ Pain crisis[2] ☐ ACS[3] ☐ Fever ☐ Acute splenic sequestration

☐ Clinical stroke ☐ Cancer ☐ Priapism ☐ Hepatic sequestration

☐ Other, specify _____

ADD

2) Has the subject had any pain crisis(es) at home[4] for which there was no hospitalization or emergency department/day hospital/urgent care visit? ☐ Yes ☐ No

→ **If yes**, how many pain crises were treated at home: _____

3) Blood Transfusion? ☐ Yes ☐ No

→ **If yes**, **click the "ADD" button and** record date and number of units or cc's for each transfusion.

Date Transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) _____ (Number) *Select one:* ☐ units ☐ cc's **OR** ☐ units/cc's unknown

Reason:

☐ Exacerbation of anemia due to an aplastic crisis ☐ Exacerbation of anemia due to splenic sequestration ☐ ACS ☐ Other complication of sickle cell disease (CNS event, priapism, AVN)

☐ Preparation for anesthesia ☐ Other, specify _____

ADD

[1] Complete AE and/or SAE forms for each reason.

[2] A pain crisis is defined here as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; requires a visit to a hospital, Emergency Department, clinic, or provider's office; and is not explained except by sickle cell disease.

[3] Acute chest syndrome is defined as a new pulmonary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, wheezing, cough, or chest pain.

[4] A painful crisis at home must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day should not be considered a painful crisis at home.

Comments for page _____

All questions relate to events since the previous visit.

Cancer

Since the previous visit, has this subject been diagnosed with cancer? ☐ Yes ☐ No

→ **If yes,** record details below and complete Adverse Event and Serious Adverse Event forms as appropriate.

Date diagnosed: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type: _____

Location: _____

ADD

Neuroimaging

Since the previous visit, has this subject undergone any neuroimaging procedures? ☐ Yes ☐ No

→ **If yes,** click the ADD button and record details for each type of test.

→ Complete one record for each type of test.

Date of test: ☐☐/☐☐☐/☐☐ (Day / Month / Year)

Type of test[1]: *(check one)* ☐ MRI ☐ MRA ☐ CT ☐ Cerebral angiography ☐ Other,specify _____

Was this result abnormal? ☐ Yes[2] ☐ No ☐ Equivocal[3]

If yes, describe brief findings: _____

_____

ADD

[1] Information about **"types of tests"** may be downloaded from the CHAMPS web page on the CSCC website.

[2] **If "result abnormal" is Yes or Equivocal**, fax results to the attention of CHAMPS at the SDMC (Rho, Inc.) 919-287-0126.

[3] **If "result abnormal" is Yes or Equivocal**, complete Adverse Event form.

Physical Exam

☐ Not Done → Specify:_____

1) Weight[1]: ☐☐☐.☐ (kg)

2) Is the spleen palpable? ☐ Yes[2] ☐ No

→ *If **yes,** what is the current spleen size?* _____ *cm*
(at the greatest distance below the left costal margin)

3) Did the subject have any new skin lesions? ☐ Yes[2] ☐ No

→ *If **yes**, where are the lesions located:* _____

4) Has subject taken any new medications since previous visit? ☐ Yes ☐ No

→ *If **yes**, complete the Concomitant Medications page:*

[1] Use the weight recorded at this visit to determine if the dose should be adjusted at the next study visit. Refer to the dosing tables in the "Study Drug" section of the Subject Study Binder.

[2] If yes, update or add to the AE page as appropriate.

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\underline{\leq}$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Early Termination** Page: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC (x10^6/mm^3)	☐.☐☐
WBC (x10^3/mm^3)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count (x10^3/mm^3)	☐☐☐☐
% Retic **OR** ARC (x10^3/mm^3)	☐☐.☐ ☐☐☐
ANC (x10^3/mm^3)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < 1000/mm^3

Platelet count < 75 x10^3/mm^3

Hb ≥ 20% ↓ from Visit 1

Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the “Labs Not Done” box and specify the reason the lab was not done.
Creatinine	Record lab results for each test using the units provided on the form: - For subjects < 18 years of age, creatinine must be ≤ 1.2 mg/dL. - For subjects ≥ 18, creatinine must be ≤ 1.4 mg/dL.
SGPT	SGPT must be < 2x the upper limit of normal.

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

☐ **Labs not done**
→*Specify:*_____

TEST	VALUE
Sodium (mmol/L)	☐☐☐
Potassium (mmol/L)	☐.☐
Chloride (mmol/L)	☐☐☐
CO_2 (mmol/L)	☐☐.☐
BUN (mg/dL)	☐☐☐
Creatinine (mg/dL)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
SGPT/ALT (U/L)	☐☐☐☐
Alk phosphatase (U/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (g/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (U/L)	☐☐☐☐

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age
Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 is life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Early Termination**
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

CRF COMPLETION GUIDELINES

Item	Instructions
Collection Date	Record the date of the sample collection and not the visit date.
Labs Not Done	If the entire lab was not completed check the Labs Not Done box and specify the reason the lab was not done.

Comprehensive Sickle Cell Centers	**Urinalysis**	**Early Termination** Page: 7 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

☐ Labs not done
→Specify:_____

Protein *(Select one, as reported by your lab)*:

☐ Negative ☐ Trace ☐ 100 ☐ 200 ☐ 300 ☐ 1+ ☐ 2+ ☐ 3+

Microscopic RBC (#/mm^3):

☐ Negative ☐ 0-5 ☐ 5-10 ☐ 10-25 ☐ 25-50 ☐ 50+

Microscopic WBC (#/mm^3):

☐ Negative ☐ 0-5 ☐ 5-10 ☐ 10-25 ☐ 25-50 ☐ 50+

* If the collection date differs from the visit date for this visit, explain: _____.

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CHAMPS Study Checklist – Study Completion

This form should be completed for all subjects who are randomized and take at least 1 dose of study drug. I.e., All subjects <u>excluding</u> screen failures; this form should not be completed for screen failures.

- Ask all Subjects who are at least 14 years of age: In your opinion, into which arm were you randomized?
  - HU & Mg. If marked:
    - Would you want to continue using HU? Yes No Don't Know
    - Would you want to continue using Mg? Yes No Don't Know
  - HU Placebo & Mg. If marked:
    - Would you want to continue using Mg? Yes No Don't Know
  - HU & Mg Placebo. If marked:
    - Would you want to continue using HU? Yes No Don't Know
  - HU Placebo & Mg Placebo
  - No opinion

- Ask the parent/guardian of all Subjects who are less than 18 years of age: In your opinion, into which arm was the subject randomized?
  - HU & Mg. If marked:
    - Would you want the subject to continue using HU? Yes No Don't Know
    - Would you want the subject to continue using Mg? Yes No Don't Know
  - HU Placebo & Mg. If marked:
    - Would you want the subject to continue using Mg? Yes No Don't Know
  - HU & Mg Placebo. If marked:
    - Would you want the subject to continue using HU? Yes No Don't Know
  - HU Placebo & Mg Placebo
  - No opinion

- Note that a subject is considered "lost to follow up" if the subject is not coming back despite several attempts by the study coordinator. This should be thoroughly documented in the Subject Binder, and requires 2 phone calls and a certified letter. Any communication (including attempts) between the site and the subject should be documented in the patient record, including requests for the return of study drug and scheduling and rescheduling study visits.
- Have PI sign the Investigator's Statement. The PI should review all study CRFs.
- A paper copy of this CRF page that includes the PI's signature and date of signature should be filed in the Subject Binder.

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CHAMPS Source Document Worksheet
For Study Completion CRF

Date: _____ / _____ / _____ **CSCC ID:** _____

NOTE: If subject lost to follow-up, include copy of certified letter in Subject Binder

Date of Last Visit: _____

Did the subject complete the study? □ Yes □ No

If no, record the date of last contact and select the **primary** reason for early withdrawal from below.

Date of Last Contact: _____

Reasons for Early Withdrawal:

- ❑ In the investigator's opinion the subject's health, safety and/or continued participation in the study
- ❑ Subject was nonadherent. *Specify:* _____
- ❑ Subject lost to follow-up
- ❑ Subject or subject's legal representative requested to withdraw *Specify:* _____
- ❑ Discontinuation *(Check all that apply)*
    - ❑ Decline in Hb level to < 5 g/dL
    - ❑ Increase in Hb level to > 13.5 g/dL (viscosity concerns)
    - ❑ Initiation of chronic transfusion
    - ❑ Hepatic dysfunction (SGPT > 2x upper limit of normal)
    - ❑ Renal toxicity (creatinine > 1.4 mg/dL)
    - ❑ Pregnancy
    - ❑ Stroke
    - ❑ Pulmonary failure requiring intubation
    - ❑ Grade 3 or 4 toxicity lasting longer than two weeks
    - ❑ Unable to orally ingest the study drug
- ❑ Other adverse event or significant concurrent illness *Specify:* _____
- ❑ Other *Specify:* _____

Investigator: In your opinion, into which arm was the subject randomized?

- ❑ HU & Mg
- ❑ HU Placebo & Mg
- ❑ HU & Mg Placebo
- ❑ HU Placebo & Mg Placebo
- ❑ No opinion

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet
For Study Completion CRF

Study Coordinator: In your opinion, into which arm was the subject randomized?

- ❑ HU & Mg
- ❑ HU Placebo & Mg
- ❑ HU & Mg Placebo
- ❑ HU Placebo & Mg Placebo
- ❑ No opinion

Subjects who are at least 14 years of age: In your opinion, into which arm were you randomized?

- ❑ HU & Mg. If marked:
  - Would you want to continue using HU? Yes No Don't Know
  - Would you want to continue using Mg? Yes No Don't Know
- ❑ HU Placebo & Mg. If marked:
  - Would you want to continue using Mg? Yes No Don't Know
- ❑ HU & Mg Placebo. If marked:
  - Would you want to continue using HU? Yes No Don't Know
- ❑ HU Placebo & Mg Placebo
- ❑ No opinion

Parent/Guardian of all Subjects who are less than 18 years of age: In your opinion, into which arm was the subject randomized?

- ❑ HU & Mg. If marked:
  - Would you want to continue using HU? Yes No Don't Know
  - Would you want to continue using Mg? Yes No Don't Know
- ❑ HU Placebo & Mg
  - Would you want to continue using Mg? Yes No Don't Know
- ❑ HU & Mg Placebo
  - Would you want to continue using HU? Yes No Don't Know
- ❑ HU Placebo & Mg Placebo
- ❑ No opinion

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

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CRF COMPLETION GUIDELINES

Item	Instructions
General	If subject misses three toxicity visits in a row, or a total of three toxicity visits and routine visits in a row, the subject should be discontinued.
Date of last visit	Record the date of the subject's last visit.
Subject Complete Study?	Indicate whether or not the subject completed the course of study drug and follow-up.
Date of last contact	Record the date of last contact with the subject.
Primary Reason	If the subject did **not** complete the study, select the **primary** reason for early withdrawal. Specify if applicable.
Discontinuation	If 'Discontinuation' is selected as the primary reason for early withdrawal, check all applicable reasons for the subject's discontinuation.

Date of last visit: ☐☐ / ☐☐☐ / ☐☐☐☐
Day Month Year

Did the subject complete the study? ☐ Yes ☐ No

→ **If no,** record the date of last contact and select the **primary** reason for early withdrawal from below.

Date of last contact: ☐☐ / ☐☐☐ / ☐☐☐☐
Day Month Year

Reasons for early withdrawal:

☐ In the investigator's opinion the subject's health, safety and/or well-being was threatened by continued participation in the study

☐ Subject was nonadherent. ***Specify:*** _____

☐ Subject lost to follow-up

☐ Subject or subject's legal representative requested to withdraw.

Specify: _____

☐ Discontinuation *(check all that apply)*

- ☐ Decline in Hb level to < 5 g/dL
- ☐ Increase in Hb level to > 13.5 g/dL (viscosity concerns)
- ☐ Initiation of chronic transfusion
- ☐ Hepatic dysfunction (SGPT > 2x upper limit of normal)
- ☐ Renal toxicity (creatinine ≥ 1.2 mg/dL if age < 18 years, creatinine ≥ 1.4 mg/dL if age ≥ 18 years)
- ☐ Pregnancy
- ☐ Stroke
- ☐ Pulmonary failure requiring intubation
- ☐ Grade 3 or 4 toxicity lasting longer than two weeks
- ☐ Unable to orally ingest the study drug

☐ Other adverse event or significant concurrent illness, ***Specify:*** _____

☐ Other, ***Specify:*** _____

CRF COMPLETION GUIDELINES

Item	Instructions
Investigator Opinion	This question should always be asked.
Study Coordinator Opinion	This question should always be asked.

Investigator:

In your opinion, into which arm was this subject randomized?

- ☐ Hydroxyurea & Magnesium
- ☐ Hydroxyurea Placebo & Magnesium
- ☐ Hydroxyurea & Magnesium Placebo
- ☐ Hydroxyurea Placebo & Magnesium Placebo
- ☐ No opinion

Study Coordinator:

In your opinion, into which arm was this subject randomized?

- ☐ Hydroxyurea & Magnesium
- ☐ Hydroxyurea Placebo & Magnesium
- ☐ Hydroxyurea & Magnesium Placebo
- ☐ Hydroxyurea Placebo & Magnesium Placebo
- ☐ No opinion

CRF COMPLETION GUIDELINES

Item	Instructions
Subject Opinion and Preference	These questions should be asked when the subject is age 14 or older. If these questions were not asked, indicate the reason they were not asked.
Parent/Guardian Opinion and Preference	These questions should be asked when the subject is less than 18 years of age. If these questions were not asked, indicate the reason they were not asked.
PI Signature	The Principal Investigator's signature is required to show that he/she has reviewed the data entries within this CRF and, to the best of his/her knowledge, the data represent a complete and accurate record of the subject's participation in the study.
Signature Date	The PI signature and date of the PI's signature is required.

Subject: Ask this question if the Subject is at least 14 years of age; skip to "Parent/Guardian" if the Subject is <14. Note that you will also ask this question of the Parent/Guardian for all Subjects under that age of 18.

In your opinion, into which arm were you randomized?

☐ Hydroxyurea & Magnesium. **If marked:**
- → Would you want to continue using Hydroxyurea? ☐ Yes ☐ No ☐ Don't know
- → Would you want to continue using Magnesium? ☐ Yes ☐ No ☐ Don't know

☐ Hydroxyurea Placebo & Magnesium. **If marked:**
- → Would you want to continue using Magnesium? ☐ Yes ☐ No ☐ Don't know

☐ Hydroxyurea & Magnesium Placebo. **If marked:**
- → Would you want to continue using Hydroxyurea? ☐ Yes ☐ No ☐ Don't know

☐ Hydroxyurea Placebo & Magnesium Placebo

☐ No opinion

☐ *Not asked, subject < 14 years old*

☐ *Not asked, other reason:*

Specify: _____

Parent/Guardian: Ask this question if the Subject is less than 18 years of age.

In your opinion, into which arm was the subject randomized?

☐ Hydroxyurea & Magnesium. **If marked:**
- → Would you want the subject to continue using Hydroxyurea? ☐ Yes ☐ No ☐ Don't know
- → Would you want the subject to continue using Magnesium? ☐ Yes ☐ No ☐ Don't know

☐ Hydroxyurea Placebo & Magnesium. **If marked:**
- → Would you want the subject to continue using Magnesium? ☐ Yes ☐ No ☐ Don't know

☐ Hydroxyurea & Magnesium Placebo. **If marked:**
- → Would you want the subject to continue using Hydroxyurea? ☐ Yes ☐ No ☐ Don't know

☐ Hydroxyurea Placebo & Magnesium Placebo

☐ No opinion

☐ *Not asked, subject ≥ 18 years old*

☐ *Not asked, parent/guardian was not present at this visit*

☐ *Not asked, other reason:*

Specify: _____

Investigator's Statement:

I have reviewed the data entries within this CRF and, to the best of my knowledge, the data represent a complete and accurate record of the subject's participation in the study.

PI signature: _____ Signature Date: ☐☐ / ☐☐☐ / ☐☐☐☐
Day / Month / Year

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CHAMPS Study Checklist – Toxicity Visit
(Weekly, when subject is experiencing a toxicity)

Toxicity Visit Tasks	Notes
❑ Hematology Panel (CBC)[1] and/or Chemistry Panel[2]	HU Toxicity: Only the labs required to evaluate the HU toxicity are required; select the Hematology Panel ***or*** the Chemistry Panel as needed. Mg Toxicity: If concerned about the effects of Mg toxicity, the local site may decide to complete chemistry and hematology lab panels.
❑ Study Drug	The study drug associated with the toxicity should be discontinued. Collect unused study drug and Study Drug Log.
❑ CRFs and EDC	▪ Hematology Labs and/or Chemistry Labs (for HU/Placebo) toxicity ▪ Toxicity Check ▪ Study Drug Record – when study drug is suspended ▪ Study Drug Administration Log – when study drug is suspended As needed: Concomitant Medications, Adverse Events / AE for Painful Crisis, Serious Adverse Events, Protocol Deviations

1) Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC
2) Sodium, Potassium, Chloride, CO2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH

<u>If the toxicity IS NOT resolved</u>

❑ Schedule another Toxicity Visit in 1 week. If this visit will take place during the window for a regular study visit, that visit will replace the Toxicity Visit.

<u>If the toxicity IS resolved</u>

❑ Use the Dosing Table to determine the new dose, adjusted for toxicity.
❑ Update the Study Drug Record and Study Drug Administration Log
❑ Administer study drug.
❑ Provide a new Study Drug Log, along with pill dispensers and dosing syringes as appropriate.

CHAMPS Source Document Worksheet
Toxicity Visit

Date: _____ / _____ / _____ **CSCC ID:** _____

Please record any other information from this visit for which there is no source document:

_____ _____

Signature *Date*

Toxicity Visit

(Unscheduled)

*** Only the pages (and/or labs) associated with the toxicity are required.**

- Hematology Labs*
- Chemistry Labs*
- Mg/Placebo Toxicity Check*
- HU/Placebo Toxicity Check*

CRF COMPLETION GUIDELINES

Item	Instructions for Hematology Labs
Collection Date	Record the date of the sample collection and not the visit date.

Item	Instructions for Electrophoresis
Hb Electrophoresis	• Record results if electrophoresis performed at this visit because of a recent transfusion. • Select “not done - no recent transfusion or Hb A (%) $\underline{\leq}$ 10 at previous visit” if no recent transfusion or if electrophoresis was not performed because Hb A (%) $\leq$ 10 at previous visit. • Select “not done – suspect Hb A (%) > 10” if electrophoresis not performed because investigator suspects value is still >10. • Central labs should not be collected until Hb A (%) $\leq$ 10.

Comprehensive Sickle Cell Centers	**Hematology Labs**	**Toxicity Visit** Page: 1 of 4
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Was a hematology lab conducted for evaluation of toxicity? ☐ Yes ☐ No

→**If yes**, complete this page.
→**If no**, leave the remainder of the page blank.

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Hemoglobin (g/dL)	☐☐.☐
Hematocrit (%)	☐☐.☐
RBC ($x10^6/mm^3$)	☐.☐☐
WBC ($x10^3/mm^3$)	☐☐.☐☐
MCV (fl)	☐☐☐.☐
MCHC (g/dL)	☐☐.☐
Platelet count ($x10^3/mm^3$)	☐☐☐☐
% Retic	☐☐.☐
OR	
ARC ($x10^3/mm^3$)	☐☐☐
ANC ($x10^3/mm^3$)	☐☐☐☐☐

ELECTROPHORESIS	
Hb A (%)	☐☐.☐ ☐ Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit ☐ Not Done - Suspect Hb A (%) > 10

HU/Placebo Toxicity Check!

ANC < $1000/mm^3$
Platelet count < $75\ x10^3/mm^3$
Hb ≥ 20% ↓ from Visit 1
Total Hb < 5 g/dL or > 13.5 g/dL

Either % Retic **OR** ARC should be provided.

Use the same unit for this subject at all study visits.

* If the collection date differs from the visit date for this visit, explain: _____.

If toxicity occurs, stop the study drug associated with the toxicity.

CRF COMPLETION GUIDELINES

Item	Instructions
All Questions	Complete Chemistry Lab if this study visit is also serving as a Toxicity Visit. Subjects will be discontinued for hepatic dysfunction or renal toxicity only if either one is not resolved with dose reduction(s) in the study drug to which the toxicities are associated (HU or Mg). This decision will be made by the site's Principal Investigator (PI). If the site's PI is concerned with the increase in creatinine level or other evidence of renal toxicity, the site's PI should bring it to the attention of the study PI, who will work with the protocol team to determine the appropriate course of action.
Collection Date	Record the date of the sample collection and not the visit date.
Creatinine	Creatinine > 1.2 mg/dL for subjects < 18 years of age, or creatinine > 1.4 mg/dL for patients $\geq$ 18 is considered a toxicity and appropriate dose reduction procedures must be followed.
SGPT	If the SGPT value is $\geq$ 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

Comprehensive Sickle Cell Centers	**Chemistry Labs**	**Toxicity Visit** Page: 2 of 4
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Was a chemistry lab conducted for evaluation of toxicity?
→ **If yes**, complete this page.
→ **If no**, leave the remainder of the page blank.

☐ Yes ☐ No

***Collection Date:** ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Creatinine (mg/dL)	☐☐.☐ ☐ Not required
SGPT/ALT (U/L)	☐☐☐☐ ☐ Not required

HU/Placebo Renal Toxicity Check
SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

If toxicity occurs, stop the study drug associated with the toxicity.

* If the collection date differs from the visit date for this visit, explain: _____.

CRF COMPLETION GUIDELINES

Item	Instructions
Diarrhea, Grade	• Grade 1 is an increase of < 4 stools/day over baseline. • Grade 2 is an increase of 4-6 stools/day over baseline **OR** IV fluids indicated < 24 hours. Diarrhea does not interfere with activities of daily life (ADL). • Grade 3 is an increase of ≥ 7 stools/day **OR** incontinence **OR** IV fluids ≥ 24 hours **OR** hospitalization. Diarrhea does interfere with ADL. • Grade 4 is life-threatening consequences (i.e., hemodynamic collapse).
Mg/Placebo Toxicity	Mark 'Yes' for "Toxicity?" if the subject has had diarrhea of grade 3 or 4 **OR** if it persists for more than 72 hours **OR** if there are signs of dehydration from diarrhea **OR** if the subject has abdominal pain severe enough to interfere with daily activities.

Comprehensive Sickle Cell Centers	**Mg/Placebo Toxicity Check**	**Toxicity Visit**
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

1) Since the last visit diarrhea has/is: ☐ Diarrhea was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If new, ongoing, or worsened:**

Grade: ☐ **1** ☐ **2** ☐ **3** ☐ **4** → *See CRF Completion Guidelines for grading criteria.*

→ *For **all Grades** complete AE form*

→ *For **Grade 3** complete SAE form if subject is hospitalized*

→ *For **Grade 4** complete SAE form*

Duration: _____days _____hours

2) Since the last visit abdominal pain has/is: ☐ Abdominal pain was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ **If ongoing, worsened, or new,** is pain severe enough to interfere with daily activities? ☐ Yes ☐ No

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→ ***If new**, add AE to AE Form*

3) Since last visit signs of dehydration have/are? ☐ Dehydration was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

→ ***If resolved** or **ongoing** modify AE Form as appropriate*

→***If new**, add AE to AE Form*

4) Does/did subject meet criteria for Mg/Placebo toxicity*? ☐ Yes ☐ No

→ ***If yes**, complete an AE Form.*

5) What action was taken with Mg/Placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the Mg/Placebo Study Drug Dosing Log*

* A toxicity exists if the subject has had diarrhea of grade 3 or 4 OR if it persists for more than 72 hours OR if there are signs of dehydration from diarrhea OR if the subject has abdominal pain severe enough to interfere with daily activities.

CRF COMPLETION GUIDELINES

Item	Instructions
Hepatic Toxicity	May not be evaluated at visits with no Chemistry Panel.
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.

Comprehensive Sickle Cell Centers	**HU/Placebo Toxicity Check**	**Toxicity Visit**
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to events <u>since the previous visit</u>.

HU/Placebo Hepatic Toxicity Check

SGPT > 2x upper limit of normal

1) Hepatic toxicity? ☐ Hepatic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Renal Toxicity Check

Creatinine ≥ 1.2 mg/dL subjects < 18 years of age

Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age

2) Renal toxicity? ☐ Renal toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

HU/Placebo Hematologic Toxicity Check *(one or more of the following)*

1. ANC < 1000/mm^3 **2. Hb** ≥ 20% ↓ from Visit 1 **3. Platelet count** < 75 x10^3/mm^3 **4. Total Hb** < 5 or > 13.5 g/dL

3) Hematologic toxicity? ☐ Hematologic toxicity was not evaluated at this visit

☐ Resolved ☐ Ongoing ☐ Worsened ☐ New ☐ Not present at this visit and was not present at the previous visit

*If any toxicity is **new**, **resolved** or **ongoing** modify AE Form as appropriate*

What action was taken with Hydroxyurea/placebo? ☐ No change ☐ Withheld ☐ Modified

→ ***If withheld or modified**, update the HU/placebo Study Drug Dosing Log*

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Comprehensive Sickle Cell Centers	**Concomitant Medications**	**Ongoing**

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	Instructions
General	Record all dates in **dd/mmm/yy** format.
Medication	Record the ***generic*** name for each concurrent medication separately in the space provided.
Indication	Record the indication for each medication.
Pre-existing?	Check if indication existed previous to study start.
Start date	Record start date or the closest approximation for any portion of a date that is unknown.
Stop date	Record stop date or the closest approximation for any portion of a date that is unknown. Leave stop date blank if medication is ongoing.
Ongoing?	Check ongoing if the subject continued on the medication after study completion or early termination. Leave stop date blank.
Information From	If the details about a medication were taken from the subject's medical record, check 'Medical record'. If the details about a medication were gathered via subject interview, check 'Interview'.

Comprehensive Sickle Cell Centers	**Concomitant Medications**	
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Record all mediations from Visit 1 to termination of study. Include start dates prior to the study **only** if the medication continues to be take at the Baseline visit.

Medication	Indication	Pre-existing	Start Date DD MMM YY	Stop Date DD MMM YY	Ongoing	Information From:
						☐ Medical record ☐ Interview
						☐ Medical record ☐ Interview
						☐ Medical record ☐ Interview
						☐ Medical record ☐ Interview
						☐ Medical record ☐ Interview
						☐ Medical record ☐ Interview
						☐ Medical record ☐ Interview
						☐ Medical record ☐ Interview

NEW

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CHAMPS Source Document Worksheet
AE for Painful Crisis

Date: _____ / _____ / _____ **CSCC ID: _____**

Since the previous study visit, has this subject experienced a painful crisis? □ Yes □ No

Note: A painful crisis is defined here as a new event, not a steady state situation. Ongoing pain at home that occurs ever day should not be recorded here as a pain crisis.

If yes, Date of onset: _____ Date of resolution: _____

Location of Pain
□ Chest
□ Back
□ Abdomen
□ Arm(s)
□ Leg(s)
□ Head & Neck

Type of Pain
□ Typical
□ Atypical

Outcome:
□ Resolved without sequelae
□ Resolved with sequelae
□ Ongoing
□ Death

Level of severity:
□ Mild - Home
□ Moderate - ER
□ Severe - Hospital Death

Relationship to study drug(s):
□ Unrelated
□ Probably not related/remote
□ Possibly related
□ Possibly related
□ Definitely related
□ Hospitalization

Action Taken:
□ No action
□ Study treatment interrupted
□ Study treatment discontinued
□ Study treatment dose adjusted
□ Concomitant medication given
□ ER/Day Hospital
□ Hospitalization

As a result of this AE, was the subject transfused? □ Yes □ No

Did the pain event evolve into another adverse event? □ Yes □ No

Please record any other information from this visit for which there is no source document:

_____ _____
Signature *Date*

Comprehensive Sickle Cell Centers	**AE for Painful Crisis**	**Ongoing**

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	Instructions
General	A painful crisis <u>at home</u> must be a new event, not a steady state situation. A pain crisis at home is defined as the occurrence of pain in the extremities, back, abdomen, chest or head that lasts at least 2 hours and is not explained except by sickle cell disease. Ongoing pain at home that occurs every day <u>should not</u> be considered a painful crisis at home. Complete this form for each painful crisis event that occurs from baseline through study termination. Do not complete an AE form unless this event evolves into another AE.
Date of Onset/ Resolution	Record the dates to indicate when the painful crisis event began and when it was resolved. If day is unknown, please estimate.
Location of pain	Check all locations where the subject experienced pain.
Type of pain	Check whether the pain experienced was 'Typical' or 'Atypical' for the subject by self report.
Outcome	Select only **one** outcome for the event. If 'ongoing', leave the stop date blank.
Severity	Select the **one** most accurate description of the event's severity.
Relationship to study drug	Select the **one** most accurate description of the relationship of the event to the study drug. See table 11.2 in the protocol for more information. • Unrelated: No temporal association; an alternative etiology has been established; event does not follow the known response pattern; event does not reappear or worsen with re-challenge. • Probably not related/remote: No temporal association; could be produced by clinical state, environment, or other intervention; event does not follow the known response pattern; event does not reappear or worsen with re-challenge. • Possibly related: Reasonable temporal association; is not readily produced by clinical state, environment, or other intervention; event follows a known response pattern <u>or</u> as yet unknown pattern of response. • Probably related: Reasonable temporal association; is not readily produced by clinical state, environment, or other intervention; event follows a known response pattern; event decreases with de-challenge. • Definitely related: Reasonable temporal association; is not readily produced by clinical state, environment, or other intervention; event follows a known response pattern; decreases with de-challenge and returns with re-challenge.
Action taken	Check **all** that apply. If study treatment was interrupted, discontinued, or adjusted, update the appropriate Study Drug Dosing Log. If a concomitant medication was given, complete the Concomitant Medication form. If the subject was hospitalized, be sure to submit a SAE form and record an entry on the appropriate Interim Health History form.

Comprehensive Sickle Cell Centers	**AE for Painful Crisis**	**Ongoing**
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Complete this form for each pain event.

Was this a Serious Adverse Event? ☐ Yes ☐ No → If yes**,** submit an SAE report to SDMC?

Date of onset: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) Date of resolution: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Location of Pain *(Check **all** that apply)*

☐ Chest ☐ Abdomen ☐ Leg(s)
☐ Back ☐ Arm(s) ☐ Head & Neck

Type of Pain

☐ Typical ☐ Atypical

What was the outcome? *(Check **one**)*

☐ Resolved without sequelae ☐ Resolved with sequelae ☐ Ongoing
☐ Present at death, not contributing to death ☐ Death due to this AE

What was the level of severity? *(Check **one**)*

☐ Mild - Home ☐ Moderate - ER ☐ Severe - Hospital

What was the relationship to study drug(s)? *(Check **one**)*

☐ Unrelated ☐ Probably not related / remote ☐ Possibly related ☐ Probably related ☐ Definitely related

What action was taken? *(Check **all** that apply)*

☐ No Action ☐ Concomitant Medication Given
☐ Study Treatment Interrupted ☐ ER/Day Hospital
☐ Study Treatment Discontinued ☐ Hospitalization
☐ Study Treatment Dose Adjusted

As a result of this AE, was the subject transfused? ☐ Yes ☐ No

→ **If yes,** complete the transfusion section of the Interim Health History form.

Did the pain event evolve into another adverse event? ☐ Yes ☐ No

→ **If yes,** complete an Adverse Event form and specify Adverse Event.

Adverse Event, specify _____

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Source Document Worksheet for AEs (non-pain)

Date: _____ / _____ / _____ **CSCC ID:** _____

☐ *** Yes** ☐ **No** Did the subject experience any adverse events (excluding pain crisis) during the study period?
If Yes, list below. *List all conditions which were not present prior to or worsened after application of study medication.*

Adverse Event/Diagnosis	Sickle Cell Related?	Start Date	Stop Date	Serious?	Outcome[1]	Severity[2]	Relation to Study Drug[3]	Actions Taken[4]
1.								
2.								
3.								
4.								
5.								

Outcome[1]
1) Resolved without sequelae
2) Resolved with sequelae
3) Medically Stable
4) Present at death, not contributing to death
5) Death
6) Ongoing

Severity[2]
1) Mild
2) Moderate
3) Severe
4) Life-threatening
5) Fatal

Relation to Study Drug[3]
1) Unrelated
2) Probably not/remote
3) Possibly related
4) Probably related
5) Definitely related

Actions Taken[4]
1) None
2) Study drug interrupted/modified
3) Study drug discontinued
4) Concomitant medication given/changed
5) Hospitalization
6) ED/Day Hospital
7) Other, specify

_____ _____
Signature *Date*

CRF COMPLETION GUIDELINES

Item	Instructions
Adverse Event	Record each adverse event separately in the space provided.
Onset Date	Record the date the adverse event began. Month and year are required date parts. If day is unknown, leave it blank and provide an override reason of unknown.
Stop Date	• Record the date the adverse event stopped. Month and year are required date parts. If day is unknown, leave it blank and provide an override reason of unknown. • If the adverse event is ongoing at the end of the study, leave the stop date blank. If the subject dies while an adverse event is ongoing, the stop date should be the date of death.
Serious Adverse Event	Check 'Yes' or 'No' to indicate if the adverse event was considered a serious adverse event. If Yes, be sure to submit a SAE report.
Outcome	• If adverse event is ongoing at end of study and subject is alive, outcome should be '3' (ongoing). • If adverse event is present at time of death, but did not contribute to subject's death, outcome should be '4'. • If adverse event is present at time of death, and **did** contribute to subject's death, outcome should be '5'.
Severity	Select the **one** most accurate description of the event's severity.
Action(s) Taken	Check **all** that apply. If study treatment was interrupted, discontinued, or adjusted, update the appropriate Study Drug Dosing Log. If a concomitant medication was given, complete the Concomitant Medication form. If the subject was hospitalized, be sure to submit an SAE form and record an entry on the appropriate Interim Health History form.

Comprehensive Sickle Cell Centers	**Adverse Events Not for Painful Crisis**	
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Click **New** on the study menu to create a new page for each AE the subject experienced during the study period.

→ If subject experienced a pain crisis, complete an *AE for Painful Crisis* page

Adverse Event / Diagnosis	Sickle Cell Related?	AE Start Date: AE Stop Date:	Serious? *If Yes, complete SAE Form*	Outcome [1]	Severity [2]	Relationship to Study Drug [3]	Action Taken [4] *Record all that apply*
1. _____	☐ N No ☐ Y Yes	☐☐/☐☐☐/☐☐☐☐ Day Month Year ☐☐/☐☐☐/☐☐☐☐ Day Month Year	☐ N No ☐ Y Yes				
2. _____	☐ N No ☐ Y Yes	☐☐/☐☐☐/☐☐☐☐ Day Month Year ☐☐/☐☐☐/☐☐☐☐ Day Month Year	☐ N No ☐ Y Yes				
3. _____	☐ N No ☐ Y Yes	☐☐/☐☐☐/☐☐☐☐ Day Month Year ☐☐/☐☐☐/☐☐☐☐ Day Month Year	☐ N No ☐ Y Yes				
4. _____	☐ N No ☐ Y Yes	☐☐/☐☐☐/☐☐☐☐ Day Month Year ☐☐/☐☐☐/☐☐☐☐ Day Month Year	☐ N No ☐ Y Yes				

[1] OUTCOME
1 = Resolved without sequelae
2 = Resolved with sequelae
3 = Medically stable
4 = Present at death, not contributing to death
5 = Death
6 = Ongoing

[2] SEVERITY
1 = Mild
2 = Moderate
3 = Severe
4 = Life-threatening
5 = Fatal

[3] RELATIONSHIP
1 = Unrelated
2 = Probably not/remote
3 = Possibly related
4 = Probably related
5 = Definitely related

[4] ACTION TAKEN
1 = None
2 = Study treatment interrupted/modified
3 = Study treatment discontinued
4 = Concomitant medication given/changed
5 = Hospitalization
6 = ER/Day hospital
7 = Other, specify

NEW

☐ Initial Report
☐ Follow-up Report # _____

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | |

Hospital code: | | |

SERIOUS ADVERSE EXPERIENCE REPORT

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) If this is a F/U, date of Initial Report

Site Name: _____ _____/_____/_____ _____/_____/_____

Subject's Date of Birth:_____

Subject's Weight: ___ ___ ___ lbs./ kgs. Subject's Gender: ☐ Male ☐ Female

Please indicate SAE category from the following choices:

- ❑ Death
- ❑ Immediately Life-Threatening
- ❑ Persistent/Significant Disability/ Incapacity
- ❑ Hospitalization/Prolonged Hospitalization
- ❑ Congenital Anomaly/Birth Defect
- ❑ Serious as assessed by the Investigator

STUDY PRODUCT DATA

Complete the Table below.

Study Product Name	Dose, Route, Schedule of Study Product(s) at SAE Onset*	Study Product Start Date (DD/MMM/YYYY)	Study Product Stop Date (DD/MMM/YYYY)
Hydroxyurea/ Placebo			☐ Ongoing
Magnesium Pidolate/ Placebo			☐ Ongoing

* Document the complete dosing schedule the subject has received in the event summary on p 2.

Event (Keyword or Cause of Death)	Date of Onset (DD/MMM/YYYY)	Severity (Select only one)	Relationship to Study Product (Select only one)	If NOT RELATED, what is the event related to:
_____	____/_____/_____	☐ Grade 1 (Mild) ☐ Grade 2 (Moderate) ☐ Grade 3 (Severe) ☐ Grade 4 (Life-Threatening) ☐ Grade 5 (Death)	☐ Unrelated ☐ Probably not/Remote ☐ Possibly ☐ Probably ☐ Definitely	☐ study procedure? specify_____ ☐ other condition/illness? specify_____ ☐ other drug? specify_____

Study Product Status

As a result of the event described above. Check one item only in each column.

Hydroxyurea/Placebo	Magnesium Pidolate/Placebo
☐ Study Product Administration Complete	☐ Study Product Administration Complete
☐ Study Product Administration Continuing	☐ Study Product Administration Continuing
☐ Study Product Administration Deferred	☐ Study Product Administration Deferred
☐ Dose Adjust *Specify*: _____ _____	☐ Dose Adjust *Specify*: _____ _____
☐ Participation terminated by Investigator	☐ Participation terminated by Investigator
☐ Other, *specify:* _____	☐ Other, *specify:* _____

Subject Status/Outcome

☐ Ongoing

☐ Resolved without sequelae Date ____/_____/_____ (DD/MMM/YYYY)

☐ Resolved with sequelae Date____/_____/_____ (DD/MMM/YYYY)

State sequelae: _____

☐ Death

Autopsy:
☐ Not Done
☐ Done (Provide Report)
☐ Planned
☐ Status Unknown

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Include supporting documentation. Then e-mail CHAMPS_SAE@RhoWorld.com noting that an SAE form has been faxed; include CSCC ID number.

☐ Initial Report
☐ Follow-up Report # _____

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | |

Hospital code: | | |

SERIOUS ADVERSE EXPERIENCE REPORT

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Site Name: _____ Report Date (DD/MMM/YYYY) _____/_____/_____ If this is a F/U, date of Initial Report _____/_____/_____

EVENT SUMMARY

Include clinical history of event, associated signs and symptoms, alternative etiologies being considered, medical management and relevant past medical history below, or attach summary. (Use additional pages if necessary.)

_____

_____

_____

_____

_____

_____

_____

_____

LABORATORY TESTS (EX: CBC, Chemistry)

List relevant abnormal lab results AND attach copies of the lab results AND indicate pertinent results on the copy. (Use additional pages if necessary.) ☐ Summary Attached?

Test	Collection Date (DD/MMM/YYYY)	Abnormal Result	Normal Range	Lab Value Previous to this SAE	Collection Date

DIAGNOSTIC TESTS (EX: MRI, CT Scan, Ultrasound)

List abnormal diagnostic test results AND attach copies of the diagnostic results AND indicate pertinent results on the copy. (Use additional pages if necessary.) ☐ Summary Attached?

Test	Date Performed (DD/MMM/YYYY)	Results/Comments

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Include supporting documentation. Then e-mail CHAMPS_SAE@RhoWorld.com noting that an SAE form has been faxed; include CSCC ID number.

☐ Initial Report
☐ Follow-up Report # _____

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | |

Hospital code: | | |

SERIOUS ADVERSE EXPERIENCE REPORT

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

If this is a F/U, date of Initial Report _____/_____/_____

Site Name: _____

CONCOMITANT MEDICATIONS

☐ No relevant concomitant medications

List relevant concomitant medications the subject was taking up to 1 month prior to SAE onset. If the subject was taking more than 6 medications, please make additional copies of this form and report all concomitant medications.

Medication (generic name)	Start Date	Stop Date	Dose	Indication	Suspect
1.	___/_____/____ DD/MMM/YYYY	___/_____/____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No
2.	___/_____/____ DD/MMM/YYYY	___/_____/____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No
3.	___/_____/____ DD/MMM/YYYY	___/_____/____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No
4.	___/_____/____ DD/MMM/YYYY	___/_____/____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No
5.	___/_____/____ DD/MMM/YYYY	___/_____/____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No
6.	___/_____/____ DD/MMM/YYYY	___/_____/____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No

Completed by (signature): _____ Completed by (print): _____ Date: ___/___/____

Investigator (signature): _____ Investigator (print): _____ Date: ___/___/____

Date Submitted/Faxed To:	(DD/MMM/YYYY)	
☐ IRB	____ / ____ / _____	☐ Not Applicable
☐ CSCC - DSMB	____ / ____ / _____	☐ Not Applicable
☐ Other, *specify:*_____	____ / ____ / _____	☐ Not Applicable

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Include supporting documentation. Then e-mail CHAMPS_SAE@RhoWorld.com noting that an SAE form has been faxed; include CSCC ID number.

☐ Initial Report
☐ Follow-up Report # _____

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | |

Hospital code: | | |

SERIOUS ADVERSE EXPERIENCE REPORT

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

If this is a F/U, date of Initial Report _____/_____/_____

Site Name: _____

Additional Information: EVENT SUMMARY

Include clinical history of event, associated signs and symptoms, alternative etiologies being considered, medical management and relevant past medical history below, or attach summary. (Use additional pages if necessary.)

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Completed by (signature): _____ Completed by (print): _____ Date: ___/___/____

Investigator (signature): _____ Investigator (print): _____ Date: ___/___/____

Date Submitted/Faxed To:	(DD/MMM/YYYY)	
☐ IRB	____ / ____ / _____	☐ Not Applicable
☐ CSCC - DSMB	____ / ____ / _____	☐ Not Applicable
☐ Other, *specify:*_____	____ / ____ / _____	☐ Not Applicable

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Include supporting documentation. Then e-mail CHAMPS_SAE@RhoWorld.com noting that an SAE form has been faxed; include CSCC ID number.

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CRF COMPLETION GUIDELINES

Item	Instructions
Date of Protocol Deviation or date when deviation was discovered	Enter the date of the protocol deviation or the date when the deviation was discovered.
Subject Randomized?	Check 'Yes' or 'No' to indicate whether the subject was randomized.
Type of Deviation	Check the one box which indicates the type of protocol deviation.
Randomization or Masking Error	If checked, specify.
Dosing Error	• If checked, specify. • Check 'Yes' or 'No' to indicate if this deviation resulted in an overdose.
Missed Visit	• If checked, indicate which visit was missed. • If checked, indicate why the visit was missed.
Mistimed Visit	• If checked, indicate which visit was mistimed. • If checked, indicate how far outside the visit window the visit was.
Mistimed Procedure or Laboratory Measure	• If checked, indicate for which visit the assessment was mistimed. • Check 'Yes' or 'No' to indicate if the entire visit was mistimed. • If 'No' is checked, indicate which part of the assessment was mistimed. • If 'Yes' is checked, specify which assessment was mistimed.
Inclusion Criteria Not Met	If checked, specify 'Inclusion Number'.
Exclusion Criteria Not Met	If checked, specify 'Exclusion Number'.

Comprehensive Sickle Cell Centers	**Protocol Deviation Form**	**Ongoing** Page 1a of 1
Hydroxyurea & Magnesium Pidolate (CHAMPS)	Date Form Completed: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) Form Completed by: ☐☐☐	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Complete a separate form for each deviation from the protocol.

Date of protocol deviation or date when deviation was discovered: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Was the subject Randomized? ☐ No ☐ Yes

Type of Deviation:

☐ **1. Randomization or Masking Error**, **Specify:**

_____

☐ **2. Dosing Error**, **Specify:** _____

Did this lead to an overdose? ☐ No ☐ Yes

☐ **3. Missed Visit, Record the Visit Number:** _____

Why was the visit missed?

- ☐ Caregiver was ill
- ☐ Transportation problems
- ☐ Scheduling difficulties
- ☐ Subject experienced AE requiring hospitalization
- ☐ Subject experienced AE requiring visit to Clinic or Physician's office
- ☐ Subject experienced AE requiring Emergency Dept/Day Hospital/Urgent Care visit
- ☐ Subject experienced AE not requiring medical attention
- ☐ Other, specify_____

(If visit was missed due to AE, be sure to complete AE & SAE forms as appropriate.)

☐ **4. Mistimed Visit, Record the Visit Number:** _____

Did the visit occur too early or too late? ☐ Too early ☐ Too late

How far outside the visit window was the visit? _____ days

☐ **5. Mistimed Procedure or Laboratory Measure, Record the Visit Number:** _____

Was the entire assessment mistimed?

- ☐ No: Which part of the assessment was mistimed? _____
- ☐ Yes: Which assessment was mistimed? _____
  (drop-down, write in the title from CRF)

☐ **6. Missed Procedure or Laboratory Measure:**

Was the entire assessment missed?

- ☐ No: Which part of the assessment was missed? _____
- ☐ Yes: Which assessment was missed? _____
  (drop-down, write in the title from CRF)

CRF COMPLETION GUIDELINES

Item	Instructions
Informed Consent	If checked, provide an explanation.
Other	If checked, specify the type of protocol violation. Provide details as appropriate.
Reason for Deviation	Explain why the deviation occurred.
Steps Taken to Resolve and Prevent Recurrence of Deviation	Explain steps taken to resolve and prevent recurrence of deviation.
Adverse Experience	• Check 'Yes' or 'No' to indicate whether this deviation resulted in an adverse experience. • If 'Yes', ensure that a corresponding entry has been added to the Adverse Events form.
Study Continuation	• Check 'Yes' or 'No' to indicate whether the subject will continue the study. • If 'No', ensure that the discontinuation form has been completed.
IRB Report	• Check 'Yes' or 'No' to indicate whether notification of this deviation is required by the IRB. • If 'Yes', provide the date on which the deviation was reported.
Further Action	If further action is required, describe it.
Additional Comments	Provide additional comments if necessary.

☐ **7. Inclusion Criteria Not Met**

Inclusion Number _____ _____ _____ (drop-down, 1-6)

☐ **8. Exclusion Criteria Not Met**

Exclusion Number _____ _____ _____ (drop-down, 1-9)

☐ **9. Informed Consent, Explain:** _____

_____

☐ **10. Other, Specify:** _____

_____

Reason for Deviation: _____

_____

_____

Steps Taken to Resolve and Prevent Recurrence of Deviation:

_____

_____

_____

Did this deviation result in an adverse experience? ☐ No ☐ Yes (*If yes, complete AE form.)*

→ If yes, was the AE serious? ☐ No ☐ Yes (*If yes, complete SAE form.)*

Will the subject continue with the study? ☐ No ☐ Yes (*If no, complete discontinuation form.)*

Is report to IRB required for this deviation? ☐ No ☐ Yes

→ If yes, Date reported: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

If further action is required, describe it: _____

_____

_____

Additional Comments: _____

_____

_____

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: ☐☐☐☐☐☐☐

Center code: ☐☐☐

Hospital code: ☐☐☐

PREGNANCY NOTIFICATION FORM - Initial Report

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

Subject's Date of Birth:_____ Subject's Weight: ___ ___ ___ lbs./ kgs. Subject's Gender: ☐ Male ☐ Female

STUDY DRUG INFORMATION

Study Product Name	Dose at Conception	Batch #	Time of Exposure			Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)
			Preconception	Trimester	Delivery		
Hydroxyurea/ Placebo capsules (PO)	_____ mg _____ mg/kg/day		☐	☐ 1 ☐ 2 ☐ 3	☐		
Magnesium Pidolate/ Placebo (PO BID)	_____ mEq _____ mg/kg/day		☐	☐ 1 ☐ 2 ☐ 3	☐		

* Document the complete dosing schedule the subject has received in the event summary on p 2.

CONCOMITANT MEDICATIONS ☐ No relevant concomitant medications

List relevant medications taken before and during pregnancy. If father exposed, enter medication taken prior to conception only..

Medication (generic name)	Start Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Dose	Indication	Suspect
1.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
2.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
3.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
4.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
5.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No

PREGNANCY INFORMATION

LMP Date: ___/_____/____

Date of Last Negative Pregnancy Test: ___/_____/____

Estimated Date of Delivery: ___/_____/____

Was estimated date corrected based on ultrasound? (Based on LMP)

Yes ☐ No ☐ N/A ☐

If "Yes" provide corrected date of delivery: ___/_____/____

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | | |

Hospital code: | | | |

PREGNANCY NOTIFICATION FORM - Initial Report

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

MATERNAL MEDICAL HISTORY

Contraception (may choose more than one)				**Number of Previous**		**Risk Factors/ Medical History**	
None	☐	Condom	☐	Pregnancies	_____	Unknown	☐
Contraceptive Medication	☐	Surgical Sterilisation (Male)	☐	Therapeutic Abortions	_____	Alcohol	☐
Diaphragm	☐	(Female)	☐	Spontaneous Abortions	_____	**Allergies***	☐
IUD	☐	Withdrawal	☐	Stillbirth	_____	**Diabetes***	☐
Infertility (Male)	☐	Rhythm	☐	Deliveries	_____	**Infection***	☐
(Female)	☐	Unknown	☐	Babies born with defects*	_____	Smoking	☐
Spermicide	☐	Withdrawal	☐			Drug abuse	☐
						Other/Relevant History	☐

Details: For all * items above, please provide details including dates & outcome as applicable.

_____

_____

_____

_____

_____

Was there a family history of birth defects? Yes ☐ No ☐ N/A ☐ If yes, describe the defects below:

_____

_____

_____

PATERNAL INFORMATION

Was there a family history of birth defects? Yes ☐ No ☐ N/A ☐ If yes, describe the defects below:

_____

_____

_____

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | | |

Hospital code: | | | |

PREGNANCY NOTIFICATION FORM - Initial Report

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

PREGNANCY STATUS (Check all that apply)

Pregnancy Ongoing	☐	Premature Delivery	☐	Spontaneous abortion[1]	☐	Ectopic Pregnancy	☐
Vaginal Delivery	☐	Stillbirth	☐	Threatened abortion[2]	☐	Unknown	☐
C-section	☐	Therapeutic abortion[3]	☐	Missed abortion[4]	☐	Other (Provide details below)	☐
Forceps	☐	Elective termination	☐				

1. Please submit an SAE form.

2. A threatened abortion is a condition of pregnancy, occurring before the 20th week of gestation, that suggests potential miscarriage may take place.

3. A missed abortion is when the embryo or fetus has died, but a miscarriage has not yet occurred.

4. Therapeutic abortion: Therapeutic abortion is defined as the termination of pregnancy before fetal viability in order to preserve maternal health. (eMedicine.com)

Signature: _____ Date of Signature: _____

Print Name: _____

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | | |

Hospital code: | | | |

PREGNANCY FOLLOW-UP FORM

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

PREGNANCY STATUS (Check all that apply)

Pregnancy Ongoing	☐	Premature Delivery	☐	Spontaneous abortion[1]	☐	Ectopic Pregnancy	☐
Vaginal Delivery	☐	Stillbirth	☐	Threatened abortion[2]	☐	Unknown	☐
C-section	☐	Therapeutic abortion[3]	☐	Missed abortion[4]	☐	Other (Provide details below)	☐
Forceps	☐	Elective termination	☐				

1. Please submit an SAE form.
2. A threatened abortion is a condition of pregnancy, occurring before the 20th week of gestation, that suggests potential miscarriage may take place.
3. A missed abortion is when the embryo or fetus has died, but a miscarriage has not yet occurred.
4. Therapeutic abortion is defined as the termination of pregnancy before fetal viability in order to preserve maternal health. (eMedicine.com)

RELEVANT LABORATORY TESTS/PROCEDURES PRE AND POST OUTCOME (e.g., Amniocentesis, ultrasound, MSAFP)

	Tests	Results Including units & normal values if applicable	Pending	Pre/Post Outcome?	Date DD/MMM/YYYY
1	_____	_____	☐	Pre ☐ Post ☐	_____
2	_____	_____	☐	Pre ☐ Post ☐	_____
3	_____	_____	☐	Pre ☐ Post ☐	_____

Further details: _____

_____

PREGNANCY OUTCOME

Infant/Fetal Outcome:

Unknown	☐	
Lost to follow-up	☐	
Number of infants/fetuses		(In the event of more than 1 infant/fetus, complete Infant Information section on a separate form for each infant/fetus.)
Normal baby	☐	
Normal fetus	☐	
Birth defect (structural/chromosomal)	☐	
Other disorder (non-structural, premature birth)	☐	
Death	☐	Date: _____ Cause of death:

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

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PREGNANCY FOLLOW-UP FORM

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Report Date (DD/MMM/YYYY) _____/_____/_____

CONCOMITANT MEDICATIONS

☐ No relevant concomitant medications

List relevant medications taken before and during pregnancy. If father exposed, enter medication taken prior to conception only..

Medication (generic name)	Start Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Dose	Indication	Suspect
1.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
2.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
3.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
4.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
5.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No

INFANT INFORMATION

Infant/Fetal Outcome:

Gender	Weight:	Length:	Head Circumference:
Male ☐	_____ lbs	_____ inch	_____ inch
Female ☐	_____ kgs	_____ cm	_____ cm

Gestational Age at Delivery/Abortion _____ (weeks)

Apgar Scores 1 minute _____ 5 minutes _____ 10 minutes _____

HIV -1 Status: Negative ☐ Positive ☐ Unknown ☐

Were there any unusual features about the pregnancy or its outcome? Yes ☐ No ☐

If Yes, specify: _____

_____

_____

_____

Follow-up Examination of the Child:

Date:_____ Findings: _____

_____

_____

_____

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Report Date (DD/MMM/YYYY) _____/_____/_____

RELEVANT LABORATORY TESTS/PROCEDURES FOR BABY/FETUS

	Tests	Results Including units & normal values if applicable	Pending	Date DD/MMM/YYYY
1			☐	
2			☐	
3			☐	
4			☐	

BIRTH DEFECT INFORMATION (Continue on Supplementary Form if necessary)

Were any birth defects noted? Yes ☐ No ☐ (If yes, complete information below.)

	Description of Birth Defect(s)	Attributable to ARV treatment? Y=Yes N=No U=Unknown	Other contributing factors: MA=Maternal Age U=Unknown O=Other
1			
2			
3			
4			

FETAL LOSS INFORMATION (Still birth, spontaneous, or abortion)

If a fetal loss occurred, were there factors, other than birth defects(s), that may have had an impact on the loss?
Yes ☐ No ☐ If yes, describe below.)

_____

_____

_____

ADDITIONAL INFORMATION (Continue on Supplementary Form if necessary)

_____

_____

_____

Signature: _____ Date of Signature: _____

Print Name: _____

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SUPPLEMENTARY INFORMATION FORM FOR PREGNANCY FOLLOW-UP FORM

ADDITIONAL INFORMATION (Optional):

_____

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Signature: _____ Date of Signature: _____

Print Name: _____

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.