

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

Table of Activities by Visit

				Hematology					
Visit	Week/Timing of	Clinical	Clinical	Panel	Adverse	Pregnancy	Chemistry	Urin-	Central
#	Visit	Evaluations ¹	Outcomes ²	(CBC) ³	Events	Test	Panel ⁴	alysis	Labs⁵
		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	Х	X	Х	Х	Х		Χ
2	Baseline (Visit 1 + 1-3 wks)	Х	Х	Х	Х	Х	Х	Х	Х
3	Week 2 ± 4 days	X	Х	X	Χ	Χ			
4	Week 4 ± 4 days	X	X	X	X	Χ			
5	Week 6 ± 4 days	X	Х	X	Χ	Χ			
6	Week 8 ± 4 days	X	X	X	X	X	X		X
7	Month 3 ± 8 days	X	Х	X	X	Χ			
8	Month 4 ± 8 days	X	X	X	X	Χ	Х		X
9	Month 5 ± 8 days	X	Х	X	Х	Χ			
10	Month 6 ± 8 days	X	X	X	X	Χ	Х	Х	X
11	Month 7 ± 8 days	X	Х	X	Х	Χ			
12	Month 8 ± 8 days	X	X	X	Х	Χ	Х		
13	Month 9 ± 8 days	X	Х	Х	Х	X			
14	Mth 10 ± 8 days	X	Х	Х	Х	Χ	Х		
15	Mth 11 ± 8 days	X	Х	Х	Х	Х			Х
16	Mth 12 ± 8 days	Χ	X	Χ	X		Х	X	

<u>Notes</u>

- 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, CO₂, 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.

CSCC Comprehensive Sickle Cell Centers

Clinical OutcomesHematology Panel

Pregnancy TestToxicity Check

CHAMPS Study Visit Checklist - All Study Visits

Visit One (Week -1) Visit Four (Week 4 ± 4 days) □ Electrophoresis* Clinical Evaluations HIV Test Clinical Outcomes Clinical Evaluations Hematology Panel Clinical Outcomes **Pregnancy Test** □ Hematology Panel □ Toxicity Check 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 \Box 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

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

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Visit Nine (Month 5 ± 8 days) Visit 13 (Month 9 ± 8 days) Clinical Evaluations Clinical Evaluations Clinical Outcomes **Clinical Outcomes** □ Hematology Panel Hematology Panel Pregnancy Test **Pregnancy Test** □ Toxicity Check **Toxicity Check** Collect unused study drug and Study Drug Log Collect unused study drug and Study Drug Log Administer study drug Administer study drug Visit 10 (Month 6 ± 8 days) Visit 14 (Month 10 ± 8 days) Clinical Evaluations Clinical Evaluations Clinical Outcomes Clinical Outcomes □ Hematology Panel Hematology Panel Pregnancy Test **Pregnancy Test** □ Toxicity Check **Toxicity Check** □ Collect unused study drug and Study Drug Log Collect unused study drug and Study Drug Log Administer last monthly supply of study drug Administer study drug □ Chemistry Panel **Chemistry Panel** □ Urinalysis (U/A) Boston Lab: 2 half-full 10-mL lavender Visit 15 (Month 11 ± 8 days) vacutainers, 1 full 5-mL green vacutainer Clinical Evaluations □ Duke Lab: 1 full 5-mL lavender vacutainer **Clinical Outcomes** Hematology Panel Pregnancy Test Visit 11 (Month 7 ± 8 days) Clinical Evaluations **Toxicity Check** Clinical Outcomes Collect unused study drug and Study Drug Log Hematology Panel Boston Lab: 2 half-full 10-mL lavender Pregnancy Test vacutainers, 1 full 5-mL green vacutainer □ Toxicity Check Duke Lab: 1 full 5-mL lavender vacutainer □ Collect unused study drug and Study Drug Log Administer study drug Visit 16 (Month 12 ± 8 days) Clinical Evaluations Visit 12 (Month 8 ± 8 days) Clinical Outcomes Clinical Evaluations Hematology Panel Chemistry Panel Clinical Outcomes □ Hematology Panel Urinalysis (U/A) □ Pregnancy Test **Toxicity Check** □ Toxicity Check

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

Collect unused study drug and Study Drug Log

Administer study drugChemistry Panel

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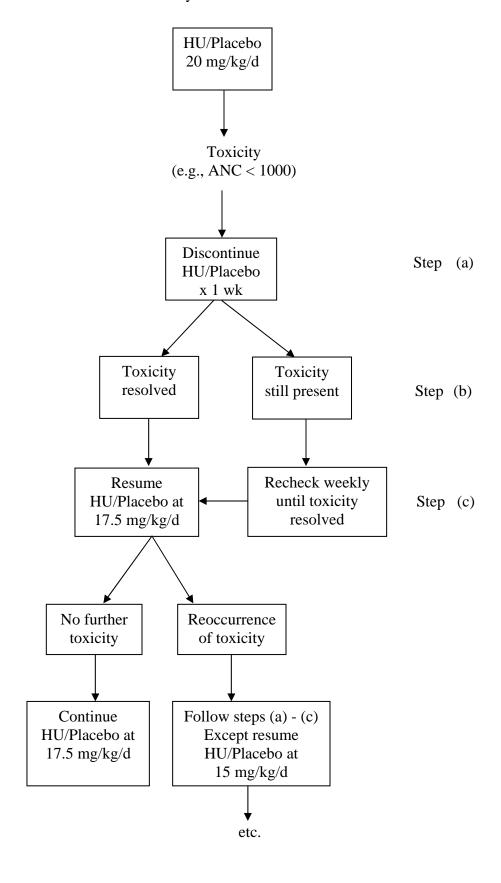
HYDROXYUREA (AND PLACEBO) DOSING AND DOSE ADJUSTMENT TABLE

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 Six, repeat).

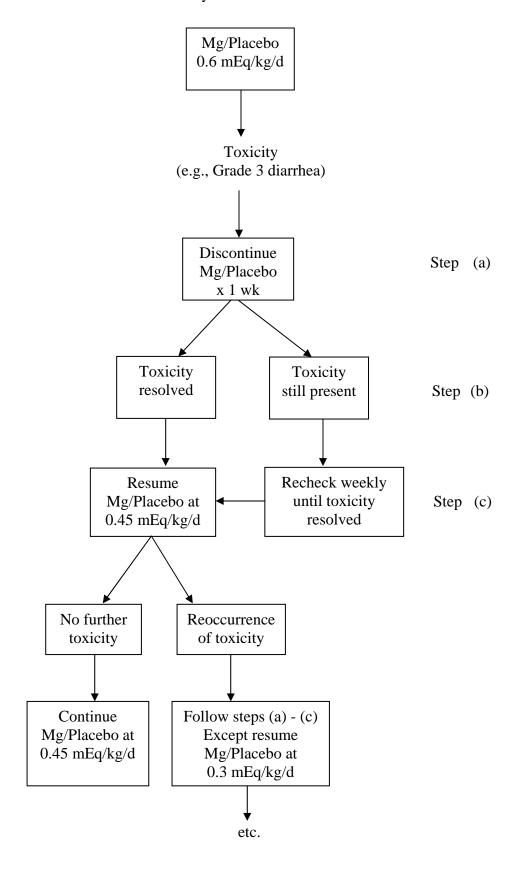
Actual doses below are close approximations of the prescribed dose. Equivalent dosing may be used if necessary. E.g., a child with a dose of 500 mg who cannot swallow the large capsules may be given alternate a dose of 400 mg with a dose of 600 mg.

		20/mg/kg/d		17.5 mg/kg/d (1 st Toxicity)		15 mg/kg/d (2 nd Toxicity)		12.5 mg/kg/d (3 rd Toxicity)					
Wt.	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		2/1/1/1/1/1/1	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



MAGNESIUM PIDOLATE (AND PLACEBO) DOSING & DOSE ADJUSTMENT TABLE

		Initial	Dose	Dose after	1 st Toxicity	Dose after 2	2 nd Toxicity
		Mg Pic		Mg Pio		Mg Pid	
Wt.	Wt. Range	0.3 mEq.		0.225 mE		0.15 mEd	
(kg)	(kg)	(mEq)	(ml)	(mEq)	(ml)	(mEq)	
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





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 Agui-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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Fax: n/a

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Email (Lab Assistant): katherine.sebastian@notes.duke.edu



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 <u>NOT</u> 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 <u>NOT</u> 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 Agui-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

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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



(Sites, please do not fax orders here)

Product Request Form

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

Sh		

Phone:

Therapak Corporation 1801 Highland Ave., Unit L

Phone: (626) 357-5900

Email: RSchulze@Therapak.com

Protocol Name: CHAMPS

Name: Emily Kunka / Cathie Snyder E-mail: Emily Kunka@rhoworld.com Duarte, CA 91010 cc: Cathie_Snyder@rhoworld.com (919) 408-8000 x 585 / x 291 Phone: Fax: (626) 357-5911 Fax: (919) 287-0126 Date Order Placed: Sponsor: **NHLBI**

Rho Project Manager:

Date Needed at Site:

Reference: Rho/CHAMPS/6203

Ship To:	Site ID:	Shipping Method:
		Freight:

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



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	Dose	Start Date	Stop Date		
(mg/kg/day)	(mg)	DD MMM YYYY	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	Dose	Start Date	Stop Date
(mg/kg/day)	(mg)	DD MMM YYYY	DD MMM YYYY
		//	/
		//	//
		/	//
		/	/
		//	/
		//	//
		//	///////
		/	///
		/	///
		/	//
		//_	//_
		/ /	/ /
			/ /
		<u> </u>	<u> </u>

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		CSCC ID: Center code:		
Pidolate (CHAMPS)		Hospital code:		

Initial Dose:

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

Dose Changed or Interrupted:

- ightarrow 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	Dose (B.I.D.)	Start Date	Stop Date
(mEq/kg B.I.D.)	(mL)	DD MMM YYYY	DD MMM YYYY
		//	//
		//	//
		/	//
		/	//
		/	//
		/	/
		/	//
		/	//
		//	//
		/	/
		/	///
		//	/
			/ /
		<u> </u>	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).

	nprehensive e Cell Centers		HU/Plac Study Drug						
Magne	Hydroxyurea & Magnesium Pidolate (CHAMPS)			Randomization Number:			SCC ID: Center code: Hospital code:		
		Dis	spense					Re	turn
Visit #	Start Date*	Not Dispensed	Bottle Number	Prescribed Dose	Capsule Type	# Capsules Dispensed/ Bottle	Returned/	Not Returned	Return Date
OR	Day Month Year			mg	200 mg 500 mg	1 1 1 1 1 1			Day Month Year
Unscheduled					200 mg				Day Month Year
									n must correspond to the or this dispensing date.
Comments									

ADD

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^{*} 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).

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.

	nprehensive e Cell Centers		Mg/Plac Study Drug		CSCC ID: Center code: Hospital code:		
Magne	Iroxyurea & esium Pidolate CHAMPS)						
				1			
		Dispens	e			Retur	n
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 mL	fl. oz.		Day Month Year
					fl. oz.		Day Month Year
					fl. oz.		Day Month Year
					NOTE: Return Infor number recorded fo		correspond to the bottle sing 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, CO₂, 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.





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 comprehe	nsive care?	□ Yes	□ No
Q6 – Is the subject in a steady state and not having	mplication of SCD?	□ Yes	□ No	
Exclusion Criteria Q3 – In the investigator's opinion, has the subject treatment regimens?	exhibited poor	adherence with previous	□ Yes	□ No
Q8 – Has the subject had treatment with an inves	tigational drug	in the last 3 months?	□ Yes	□ No
Q9 – Does the subject have any other chronic illn his/her responsiveness to study drug?	ess other than	SCD that might affect	□ Yes	□ No
Physical Exam:				
Weight kg				
Is the spleen palpable? \Box Yes \Box No If yes, w	hat is the curre	ent spleen size? cm		
Does the subject have any skin lesions? □ Yes	□ No If yes,	where are the lesions locate	ed?	
Is the subject taking any medication? List				
Medical History Complete this section only if the information was medical record. For Re-screening Visits, simply upon	pdate the infori	mation collected at Visit 1.		
Has the subject ever had or ever been diagnosed present/occurred in the last year)		red, enter year of 1 st diagno of 1 st Dx	sis and if	

	Year of 1 st 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		



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 crisi was no hospitalization or ED/day hospital/urgent care vis present in the medical record! For Re-screening Visits, scollected at Visit 1. If yes, how many pain crises: Were treated at home? Were treated in a clinic or doctor's office, not hospitalized.	sit? Only record information not simply update the information	□ Yes	□ No
Places record any other information from this visit for	or which there is no course down	nont:	
Please record any other information from this visit for	or which there is no source docur	nent:	
Signature	Date		



RhoLAB Specimen ID Tracker January 4, 2007

Subject ID Number _____ Visit Date _____ 10-mL lavender vacutainer Place here 10-mL lavender vacutainer Place here 5-mL green vacutainer Place here 5-mL lavender vacutainer

Place

here



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

Comprehensive Sickle Cell Centers

Inclusion Criteria

Visit 1

Page: 1 of 11

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	Instructions
Questions 3 and 6	Information obtained from <i>Health History</i> 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 <i>Screening</i> 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 Yes.

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 crisis¹, acute chest syndrome²) in the previous 12 months?	Yes	No No
4. Has the subject/guardian signed an informed consent/assent form?	Yes	No 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 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.

Comprehensive Sickle Cell Centers

Exclusion Criteria

Visit 1

Page: 2 of 11

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Instructions
Information obtained from the medical record.
Information obtained from the medical record. Mark 'No' if no test was performed in the previous month.
Information obtained from pregnancy test administered at entry for this visit. This question must be answered 'Yes' or 'No' for all subjects.
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.
Information obtained from medical record and subject interview.
Additional exclusion criteria are listed in the protocol. These criteria are incorporated into the CRF on the <i>Screening</i> 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

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Comprehensive Sickle Cell Centers	Exclusion Criteria V6.1	Visit 1 Page: 2 of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

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

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

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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.

Comprehensive Sickle Cell Centers

Screening

Visit 1

Page: 3a of 11

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	Visit 1 Page: 3a of 11			
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code: Hospital code:			
Expected Date of Next Visit: (Within 1 - 3 weeks of Visit 1)	Day Month Year → Email date	re to CHAMPS_labs@rhoworld.com			
1) Red Cell Density: % Hyperdense cells	. % % hyperdense cells will be provide				
2) Hemoglobin Level:	RBCs with density > 41 g/dL, he/she is eligible to continue				
·	evel between 8 – 12.5 g/dL?Yes petween 8 – 12.5 g/dL, he/she <u>is eligible</u> to continue in this				
3) Hb A %: Has the subject been transfused within the past 3 months?					
If the subject has a Hb A %	10, he/she <u>is eligible</u> to continue in this study.				
4) HIV Status: (tested within the last 12 months) Date tested: Day Month Year Result: Negative Positive					
If the subject <u>has</u> a negative HIV test, he/she <u>is eligible</u> to continue in this study.					
5) Hepatic Dysfunction: Within the past month, has the Screening SGPT level (U	ne subject had SGPT > 2x the upper limit of normal? /L) Local lab upper limit of no				
If the subject <u>has not had</u> SG study.	PT > 2x upper limit of normal within the past month, he/she	is eligible to continue in this			
6) Renal Dysfunction: Within the past month has su 1.2 mg/dL (if age 18.0 years Screening creatinine level (n	<u></u>				
If the subject <u>has not had</u> cre the past month, he/she <u>is elig</u>	atinine \geq 1.0 mg/dL (if under age 18.0 years) or \geq 1.2 mg/d ible to continue in this study.	L (if 18.0 years or above) within			

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Comprehensive Sickle Cell Centers	Screening	Visit 1 Page: 3b of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Dem	oar	anl	nics
	og.	чрі	

Date of Birth: Day Month Year	
Gender: Male Female	

Hemoglobinopathy

Date of Results: Day	Month Year
S (%)	
C (%)	Include the decimal if provided on the lab report (e.g., 24.6 or 24.0).
A (%)	If no decimal is provided on the lab report, leave the last box empty (e.g., 24); do not add a zero.
A2 (%)	
F (%)	
Other (%) O	ther, 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.

Comprehensive Sickle Cell Centers	Physical Exam	Visit 1 Page: 4 of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

	Hospital code.
hysical 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 distant	nce below the left costal margin)
3) Does the subject have any skin lesions? Yes → If yes, where are the lesions located:	□ No
4) Is the subject taking any medication? Yes → If yes, record information on the Concomitant Medications CRF. → Be sure to check "Pre-existing" on the Concomitant Medications CRF.	No cations CRF.

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

Comprehensive Sickle Cell Centers	Medical History	Visit 1 Page: 5 of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

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

1. Is the s	subject enrolled	in the C-	Data study?	Yes No	
follow → For	ing conditions.	arked "Ye	es" provide the "Year	of First Diagnosis." Also, indicate whether the	
Yes	Year of First Diagnosis	No	Unknown	Condition	If yes, Present/ Occurred in past year?
			(Muscular, (Muscular, (CNS) Strol	er	
			→ Spec (Splenic) H (Muscular, (Renal/Gen (Ocular) Re	cify: cify: lypersplenism Skeletal, Skin) Leg Ulcers initourinary) Priapism N/A, female subjectinopathy cute Splenic Sequestration	ect

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.

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Sickle Cell Centers	Modic	cal History	Vis		age: 6 of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)			cso	CC ID: Center	r code:
				Hospital	code:
ormation to be determined by patien	t interview and rev	riew of medical rec	ords.		
cer					
as the subject <u>ever had</u> or ever be	_		Yes	No	
→ If yes, list the type(s) of cancer present in the last year.	below. For each t	ype listed provide y	ear of first diagn	osis and indic	cate whether
Type of C	Cancer		Year of First Diagnosis	Prese	ent in Last Year?
				Y	res No
				Y	res No
				Y	res No
roimaging					
n the past year, has neuroimaging → If yes click the ADD button an			dings?	Yes	□ No □ N
→ If yes click the ADD button an			dings?	Yes	
→ If yes click the ADD button and Date of test: Day Month Type of test*: MRI MR	d, record details fo			Yes Other, specify	
→ If yes click the ADD button and Date of test: Day Month Type of test*: MRI MR Briefly describe the findings: Date of test: Date of test:	d, record details fo	r each test/type.			
→ If yes click the ADD button and Date of test: Day Month Type of test*: MRI MR Briefly describe the findings: Date of test: Day Month	d, record details fo	r each test/type.	ıraphy		у
Date of test: Day Month Type of test*: MRI MR Briefly describe the findings: Date of test: Day Month	d, record details fo	r each test/type.	ıraphy	Other, specify	у
→ If yes click the ADD button and Date of test: Day Month Type of test*: MRI MR Briefly describe the findings: Date of test: Day Month Type of test*: MRI MR	d, record details fo	r each test/type.	ıraphy	Other, specify	у
→ If yes click the ADD button and Date of test:	d, record details fo	r each test/type.	raphy	Other, specify	y
→ If yes click the ADD button and Date of test:	d, record details fo	Cerebral angiog	raphy	Other, specify	y
→ If yes click the ADD button and Date of test:	d, record details for Year A CT Year A CT Year A CT CT	Cerebral angiog	raphy	Other, specify	y

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Health History

Visit 1

Page: 7 of 11

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.

HLHX

Comprehensive Sickle Cell Centers	Health History	Visit 1 Page: 7a of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:
All questions relate to events	in the past 12 months.	
	<u>vents</u> that led to a visit to physician's officent care facility, or a hospitalization?	e/clinic/emergency Yes No
	atton and record information for each event.	
Treatment Location:	Date of Encounter:	
Physician's Office / Clinic	Day Month Year	
Emergency Department / Day Hospital / Urgent Car	e Day Month Year	
Date	Admitted: Date Discharg	ged:
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		
	n crisis(es) at home ⁴ for which there was n v department/day hospital/urgent care visit	
→ If yes, how many pain cris	es were treated at home:	
Complete AE and/or SAE forms for each reason IF	the event occurred after the informed consent form was signed.	

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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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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 <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.

Comprehensive Sickle Cell Centers	Health Histor	У	Visit 1 Page: 7b of 11
Hydroxyurea &			CSCC ID:
Magnesium Pidolate (CHAMPS)			Center code:
,			Hospital code:
This question relates to even	ts in the past 12 months.		
3) Blood Transfusion? [Yes No	oite or ce's for o	ageh transfusion
7 ii yes, click tile ADD but	on and record date and number of di	Select one:	acii transiusion.
Date Transfused: Day	Month Year Number	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



Hematology Labs

Visit 1

Page: 8 of 11

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 <i>Screening</i> CRF (Does the subject have an Hb level between 8.0 – 12.5 g/dL?)	

НЕМА

Comprehensive Sickle Cell Centers	Hen	natology l	_abs		Visit 1 Page: 8 of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)					CSCC ID: Center code:
					Hospital code:
*C	collection Date:	Day N	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 (x10³/mm³)		
% Retic		Either % Retic <u>OR</u> ARC should be provided.
OR ARC (x10 ³ /mm ³)		Use the same unit for this subject at all study visits.
ANC (/mm³)		

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^{*} If the collection date differs from the visit date for this visit, explain: ______.

Chemistry Labs

Visit 1

Page: 9 of 11

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	Ch	emistry Labs	Visit '	1 Page: 9 of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)			CSCC II	Center code:
				Hospital code:
*C	ollection Date:	Day Month Yea	ır	

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: ______.

Pregnancy Test

Visit 1

Page: 10 of 11

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

PREG

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 1 Page: 10 of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Pregnancy Test	
Not Done (C	heck reason below)
Subject	t male
Subject	has not reached menstruating age
Postme	nopausal
Hystere	ctomy
Tubal li	gation
Other,	specify:
*Date of Collection:	Day Month Year
Туре:	Serum Urine
Result: p	Positive Negative
L	

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

Screen Failure Log for Visit 1

Visit 1

Page: 11 of 11

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	Instructions		
General	This form should be completed the <i>first time</i> 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)

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 rescreening 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

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, & email date to CHAMPS_labs@rhoworld.com 7-10 days before Visit 2.

Screen Failures:

Complete the Screen Failure Log CRF.

²⁾ Sodium, Potassium, Chloride, CO₂, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH





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 comprehe	nsive care?	□ Yes	□ No
Q6 – Is the subject in a steady state and not having	ng an acute coi	mplication of SCD?	□ Yes	□ No
Exclusion Criteria Q3 – In the investigator's opinion, has the subject treatment regimens?	exhibited poor	adherence with previous	□ Yes	□ No
Q8 – Has the subject had treatment with an inves	tigational drug	in the last 3 months?	□ Yes	□ No
Q9 – Does the subject have any other chronic illn his/her responsiveness to study drug?	ess other than	SCD that might affect	□ Yes	□ No
Physical Exam:				
Weight kg				
Is the spleen palpable? \Box Yes \Box No If yes, w	hat is the curre	ent 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 present/occurred in the last year)		red, enter year of 1 st diagno of 1 st Dx	sis and if	

	Year of 1 st 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 □		



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 crisi was no hospitalization or ED/day hospital/urgent care vis present in the medical record! For Re-screening Visits, scollected at Visit 1. If yes, how many pain crises: Were treated at home? Were treated in a clinic or doctor's office, not hospitalized.	sit? Only record information not simply update the information	□ Yes	□ No
Places record any other information from this visit for	or which there is no course down	nont:	
Please record any other information from this visit for	or which there is no source docur	nent:	
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.

Inclusion Criteria

Re-screening – Visit 1

Page: 1 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	Instructions	
Questions 3 and 6	Information obtained from <i>Health History</i> 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 <i>Screening</i> page for this visit.	

INCL

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

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

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 crisis¹, acute chest syndrome²) 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.

Exclusion Criteria

Re-screening – Visit 1

Page: 2 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 <i>Screening</i> 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

Comprehensive	Exclusion Criteria V6.1	Re-screening – Visit 1
Sickle Cell Centers		Page: 2 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
Tidolate (OTIANII O)		Hospital code:

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

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

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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.

Screening (Re-screen)

Re-screening – Visit 1

Page: 3a of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	Screening (Re-screen)	Re-screening – Visit 1		
	Sickle Cell Centers		Page: 3a of 8		
	Hydroxyurea & Magnesium		CSCC ID: Center code:		
	Pidolate (CHAMPS)		Hospital code:		
	Expected Date of Next Visit: (Within 1 - 3 weeks of Visit 1)	Day Month Year → Email date	e to CHAMPS_labs@rhoworld.com		
1)	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:				
,	•	evel between 8 – 12.5 g/dL?	☐ No		
	If the subject has a Hb level b	netween 8 – 12.5 g/dL, he/she <u>is eligible</u> to continue in this s	study.		
3)	Hb A %: Has the subject been transfus → If yes, is the subject's Hb		No		
	If the subject has a Hb A %	10, he/she <u>is eligible</u> to continue in this study.			
4)	HIV Status: (tested within the	last 12 months)			
4)	Date tested: /	Result: Negative Month Year	Positive		
	If the subject has a negative	HIV test, he/she <u>is eligible</u> to continue in this study.			
5)	Hepatic Dysfunction:				
•	-	ne 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 <u>has not had</u> SGPT > 2x upper limit of normal within the past month, he/she <u>is eligible</u> 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 ≥ Yes No 1.2 mg/dL (if age 18.0 years or above)?					
	Screening creatinine level (n	ng/dL) Local lab upper limit of n	ormal (mg/dL)		
	If the subject <u>has not had</u> creatinine \geq 1.0 mg/dL (if under age 18.0 years) or \geq 1.2 mg/dL (if 18.0 years or above) within the past month, he/she <u>is eligible</u> to continue in this study.				

Comprehensive	Physical Exam	Re-screening – Visit 1
Sickle Cell Centers	•	Page: 4 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Not Done → Specify	
) Weight¹: (kg)	
2) Is the spleen palpable?	□ 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:	
	Yes No
l) Is the subject taking any medication?	

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



Hematology Labs

Re-screening – Visit 1

Page: 5 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

НЕМА

Comprehensive Sickle Cell Centers	Hematology Labs	Re-screening – Visit 1 Page: 5 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code: Hospital code:
*C	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 (x10³/mm³)		
% Retic		Either % Retic <u>OR</u> ARC should be provided.
OR ARC (x10 ³ /mm ³)		Use the same unit for this subject at all study visits.
ANC (/mm³)		

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^{*} If the collection date differs from the visit date for this visit, explain: ______.

Chemistry Labs

Re-screening – Visit 1

Page: 6 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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

*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: ______.

Pregnancy Test

Re-screening - Visit 1

Page: 7 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

PREG

Comprehensive	Pregnancy Test	Re-screening – Visit 1
Sickle Cell Centers	G ,	Page: 7 of 8
Hydroxyurea & Magnesium		CSCC ID: Center code:
Pidolate (CHAMPS)		Hospital code:

Pregnancy 1	Done (Check reason below)
	Subject male
	Subject has not reached menstruating age
	Postmenopausal
	Hysterectomy
	Tubal ligation
	Other, specify:
*Date of C	ollection: Day Month Year Serum Urine
Result	

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

Screen Failure Log for Re-screening – Visit 1

Re-screening – Visit 1

Page: 8 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 Rescreening 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 Rescreening Visit?	Check "Yes" or "No". If "No," specify the reason the subject is not eligible.	

Comprehensive	Screen Failure Log for	Re-screening – Visit 1
Sickle Cell Centers	Re-screening – Visit 1	Page: 8 of 8
Hydroxyurea &		CSCC ID:
Magnesium Pidolate (CHAMPS)		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 / 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?
→ 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, <i>Specify:</i>
Did subject complete the Re-screening Visit?
→ 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 two Medical History forms and the Health History form under the Visit 1 EDC link.
Is this subject eligible for the 2nd Re-screening Visit?
→ 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)

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 rescreening 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, CO₂, 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.





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 comprehe	nsive care?	□ Yes	□ No
Q6 – Is the subject in a steady state and not having	ng an acute coi	mplication of SCD?	□ Yes	□ No
Exclusion Criteria Q3 – In the investigator's opinion, has the subject treatment regimens?	exhibited poor	adherence with previous	□ Yes	□ No
Q8 – Has the subject had treatment with an inves	tigational drug	in the last 3 months?	□ Yes	□ No
Q9 – Does the subject have any other chronic illn his/her responsiveness to study drug?	ess other than	SCD that might affect	□ Yes	□ No
Physical Exam:				
Weight kg				
Is the spleen palpable? \Box Yes \Box No If yes, w	hat is the curre	ent spleen size? cm		
Does the subject have any skin lesions? □ Yes	□ No If yes,	where are the lesions locate	ed?	
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 present/occurred in the last year)		red, enter year of 1 st diagno of 1 st Dx	sis and if	

	Year of 1 st 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		



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 crisi was no hospitalization or ED/day hospital/urgent care vis present in the medical record! For Re-screening Visits, scollected at Visit 1. If yes, how many pain crises: Were treated at home? Were treated in a clinic or doctor's office, not hospitalized.	sit? Only record information not simply update the information	□ Yes	□ No
Places record any other information from this visit for	or which there is no course down	nont:	
Please record any other information from this visit for	or which there is no source docur	nent:	
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.

Inclusion Criteria

2nd Re-screening - Visit 1

Page: 1 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	Instructions	
Questions 3 and 6	Information obtained from <i>Health History</i> 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 <i>Screening</i> 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: / / / / / / / / / / / / / / / / / / /	CSCC ID: Center code:
	Day Month Year	Hospital code:

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

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 crisis¹, acute chest syndrome²) 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.

Exclusion Criteria

2nd Re-screening - Visit 1

Page: 2 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Instructions	
Information obtained from the medical record.	
Information obtained from the medical record. Mark 'No' if no test was performed in the previous month.	
Information obtained from pregnancy test administered at entry for this visit. This question must be answered 'Yes' or 'No' for all subjects.	
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.	
Information obtained from medical record and subject interview.	
Additional exclusion criteria are listed in the protocol. These criteria are incorporated into the CRF on the <i>Screening</i> 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

Comprehensive	Exclusion Criteria V6.1	2nd Re-screening – Visit 1
Sickle Cell Centers		Page: 2 of 8
Hydroxyurea & Magnesium		CSCC ID: Center code:
Pidolate (CHAMPS)		Hospital code:

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

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	
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	
 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	

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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.

Screening (Re-screen)

2nd Re-screening - Visit 1

Page: 3a of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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

Com	orehensive	Screening (Re-screen)	2nd Re-screening – Visit 1
-	Cell Centers	Corcerning (Re Sorcern)	Page: 3a of 8
Ma	oxyurea & gnesium e (CHAMPS)		CSCC ID: Center code:
			Hospital code:
-	Pate of Next Visit: 3 weeks of Visit 1)	Day Month Year → Email date	e to CHAMPS_labs@rhoworld.com
1) Red Cell D % Hyperd		% % hyperdense cells will be provide	ed via an e-mail from RhoLAB.
If the su	bject has <u>></u> 3 percent	RBCs with density > 41 g/dL, he/she is eligible to continue	in this study.
2) Hemoglob	in Level:		
Does the	subject have a Hb	evel between 8 – 12.5 g/dL?	No
If the su	bject <u>has</u> a Hb level i	petween 8 – 12.5 g/dL, he/she <u>is eligible</u> to continue in this	study.
3) Hb A %:			
Has the su	bject been transfu	sed within the past 3 months?	No
→ If yes,	is the subject's HI	o A <u><</u> 10%? ☐ Yes ☐ No	
If the su	bject <u>has</u> a Hb A %	≤ 10, he/she <u>is eligible</u> to continue in this study.	
4) HIV Status	: (tested within the	e last 12 months)	
Date test	L	Result: Negative	Positive
If the su	bject <u>has</u> a negative	HIV test, he/she <u>is eligible</u> to continue in this study.	
5) Hepatic Dy	sfunction:		
Within the	past month, has t	ne subject had SGPT > 2x the upper limit of normal?	Yes No
Screer	Screening SGPT level (U/L) Local lab upper limit of normal (U/L)		
If the su	If the subject <u>has not had</u> SGPT > 2x upper limit of normal within the past month, he/she <u>is eligible</u> to continue in this study.		
6) Renal Dys	6) Renal Dysfunction:		
	Within the past month has subject had creatinine ≥ 1.0 mg/dL (if under age 18.0 years) or ≥		
Screening	Screening creatinine level (mg/dL) Local lab upper limit of normal (mg/dL) .		
	If the subject <u>has not had</u> creatinine \geq 1.0 mg/dL (if under age 18.0 years) or \geq 1.2 mg/dL (if 18.0 years or above) within the past month, he/she <u>is eligible</u> to continue in this study.		

Comprehensive Sickle Cell Centers	Physical Exam	2nd Re-screening – Visit 1 Page: 4 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

	Hospital code:
ysical 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)
	(at the greatest distance selent the left destail 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 Concomi	itant 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.



Hematology Labs

2nd Re-screening - Visit 1

Page: 5 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 <i>Screening</i> CRF (Does the subject have an Hb level between 8.0 – 12.5 g/dL?)	

НЕМА

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 (x10³/mm³)		
% Retic		Either % Retic OR ARC should be provided.
OR ARC (x10 ³ /mm ³)		Use the same unit for this subject at all study visits.
ANC (/mm³)		

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^{*} If the collection date differs from the visit date for this visit, explain: ______.

Chemistry Labs

2nd Re-screening - Visit 1

Page: 6 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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

*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: ______.

Pregnancy Test

2nd Re-screening - Visit 1

Page: 7 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

PREG

Comprehensive	Pregnancy Test	2nd Re-screening – Visit 1
Sickle Cell Centers	,	Page: 7 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

_	
nancy Test	
Not Done (Ch	eck reason below)
Subject	male
Subject	nas not reached menstruating age
Postmer	opausal
Hystered	tomy
Tubal lig	ation
Other, s	pecify:
Date of Collection:	Day Month Year
Type: S	erum Urine
Result: P	ositive Negative

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

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Screen Failure Log for 2nd Re-screening – Visit 1

2nd Re-screening - Visit 1

Page: 8 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	Instructions
General	This form should be completed the <i>third time</i> 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 Rescreening 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.

Comprehensive Sickle Cell Centers	Screen Failure Log Re-screening –		2nd Re-screening – Vi	
Hydroxyurea & Magnesium Pidolate (CHAMPS)			CSCC ID: Center code:	
			Hospital code:	
	mpleted the <i>third time</i> the subjec ger eligible for this study.	t discontinues p	rior to receiving study drug.	
Date of last study related cor	ntact: Day Month /	Year		
Primary Reason the subject	will not be enrolled: (Check only	one.)		
would be threatened b	oinion, the subject's health, safety a by participation in the study.	nd/or well-being		
Subject lost to follow-u				
Subject or subject's le	gal representative requested to with	ndraw. Specify: _		
Subject did not meet in	nclusion/exclusion criteria.			
Is subject no longer in	steady state after previously meeti	ng inclusion/exclu	ısion criteria? Yes	No
→ If Yes, check all that	at apply and complete the Adverse	Event forms.		
☐ Subject e	experienced one or more vaso-occlu	isive crises		
	experienced one or more non-vaso-		vents	
	experienced one or more non-sickle			
Other Reason, Specif				
Did subject complete the 2nd	_	es		
	le the Date of Informed Consent at <u>ledical History</u> forms and the <u>Health</u>			
Date of Informed C	Consent: Day / Month /	Year		
→ If yes, be sure to o	omplete all 2nd Re-screening CRFs	S.		
Investigator's Statement:				
	tries within this CRF and, to the beard of the subject's participation in the		re, the data represent a	
PI signature:	Sign	nature Date: Day	Month Year	



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

Clinica	Visit Two Tasks	Notes	
	Randomize subject	File randomization e-mail in Subject Binder.	
	<u> </u>	·	
	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

1 week after this visit:

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

²⁾ Sodium, Potassium, Chloride, CO2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH



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
is the subject taking any medication: List
Please record any other information from this visit for which there is no source document:
Signature Date



RhoLAB Specimen ID Tracker January 4, 2007

Subject ID Number _____ Visit Date _____ 10-mL lavender vacutainer Place here 10-mL lavender vacutainer Place here 5-mL green vacutainer Place here 5-mL lavender vacutainer

Place

here



CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

Visit Two

(Baseline 1-3 Weeks)

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

Interim Health History

Visit 2

Page: 1 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 click the 'ADD' button for each location</u>. 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 event	s since the previous study visit.	
department/day hospital/urg	events that led to a visit to physician's office/clinic gent care facility, or a hospitalization? utton and record information for each event	c/ emergency Yes No
Treatment Location:	Date of Encounter:	
Physician's Office / Clinic	Day Month Year	
Emergency Department / Day Hospital / Urgent Ca	re Day Month Year	
Date Hospital /	Admitted: Date Discharged:	
Reason(s) ¹ :	Month Year Day Month Ye	L laar
Pain crisis ²	ACS ³ Fever Ac	ute splenic sequestration
Clinical stroke	Cancer Priapism He	patic sequestration
Other, specify		
hospitalization or emergen	in crisis(es) at home ⁴ for which there was no cy department/day hospital/urgent care visit?	Yes No
3) Blood Transfusion?	Yes No	
→ If yes, click the "ADD" b	utton and record date and number of units or cc's fo	r each transfusion.
Date Transfused: Day	Select one: Units Number Cc's	OR units/cc's unknown
Reason: Exacerbation of anemia due to an aplastic crisis	Exacerbation of anemia ACS due to splenic sequestration	Other complication of sickle cell disease (CNS event, priapism, AVN)
Preparation for anesthesia	Other, specify	
Emergency Department, clinic, or provider's office	pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; and is not explained except by sickle cell disease. hary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, whe	

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Comments for page

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⁴ 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.

Comprehensive Sickle Cell Centers	Interim Health History	Visit 2 Page: 2 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

All questions relate to events since the previous v	visit.			
ncer				
ce Visit 1, has this subject been diagnosed w	rith cancer?	Yes	☐ No	
If yes, record details below and complete Adve	erse Event and Serious	Adverse Event for	rms as appropriate.	
Date diagnosed: Day Month	Type: Year Location			
				ADE
roimaging				
ce Visit 1, has this subject undergone any ne If yes, click the ADD button and record details		es?	Yes No	
 If yes, click the ADD button and record details → Complete one record for each type of test. Date of test: / 	for each type of test.	es?	Yes No	
 If yes, click the <u>ADD</u> button and record details → Complete one record for each type of test. 	for each type of test.	ebral iography	Yes No Other,specify	
If yes, click the ADD button and record details → Complete one record for each type of test. Date of test: Day Month Year Type of test¹: MRI MRA	for each type of test. CT Cer ang No Equ	ebral	Other,specify	

- 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.

Comprehensive Sickle Cell Centers	Physical Exam	Visit 2 Page: 3 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

nysical Exam			
Not Done → Specify:			
1) Weight ¹ : (kg)			
2) Is the spleen palpable? ☐ Yes² → If yes, what is the current spleen size?	No cm (at the greatest distance below the left costal margin)		
3) Did the subject have any new skin lesions? → If yes, where are the lesions located:	Yes ² No		
4) Has subject taken any new medications since previous visit?			

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.

 $^{^{2}\,\}mathrm{lf}$ yes, update or add to the AE page as appropriate.

Hematology Labs

Visit 2

Page: 4 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 rea 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

Comprehensive Sickle Cell Centers	Hematology Labs			Visit 2	Page: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)				CSCC ID:	Center code:
				1	Hospital code:
*C	ollection Date:	Day Month	Year		
Labs not don → Specify:	e				
7 Зреспу					
	_				
TES	ЭТ 	VALUE			
Hemoglobin (g/d	dL)				
Hematocrit (%)					
RBC (x10 ⁶ /mm ³)				
WBC (x10 ³ /mm	³)				
MCV (fl)					
MCHC (g/dL)					
Platelet count (x	:10 ³ /mm ³)				
% Retic			_	Either %	Retic <u>OR</u> ARC should be provided.
OR ARC (x10 ³ /mm ³)		-		same unit for this subject at all study visits.
ANC (x10 ³ /mm ³)				

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

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Chemistry Labs

Visit 2

Page: 5 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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

Comprehensive Sickle Cell Centers	Chemistry Labs	Visit 2 Page: 5 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
Tidolate (OTIANII O)		Hospital code:
*C	Day Month Year	
Labs not don → Specify:	е	

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: ______.

Urinalysis

Visit 2

Page: 6 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 Page: 6 of 7
Hydroxyurea & Magnesium		CSCC ID: Center code:
Pidolate (CHAMPS)		Hospital code:
*C	Day Month Year	
☐ Labs not do	ne	
Γ		
Protein (Select one, as re	eported by your lab):	
Negative 1	frace 100 200 300 1+	2+ 3+
Microscopic RBC (#/mn	n³):	
Negative C	-5 5-10 10-25 25-50	50+
Microscopic WBC (#/m	m³):	
Negative C	-5 5-10 10-25 25-50	<u>50+</u>

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

Pregnancy Test

Visit 2

Page: 7 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

PREG

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 2 Page: 7 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

onov To	
nancy Tes	
Not Do	ne (Check reason below)
□ S	ubject male
S	ubject has not reached menstruating age
P	ostmenopausal
☐ H	ysterectomy
Пт	ubal ligation
□ o	ther, specify:
_	
Date of Colle	ection: Day Month Year
Туре:	Serum Urine
Result:	Positive Negative

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



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 Panel²
- Chemistry Lab CRF
- 2) Sodium, Potassium, Chloride, CO₂, 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.



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
is the subject taking any medication: List
Please record any other information from this visit for which there is no source document:
Signature Date

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

Visit Three

(Week 2 +/- 4 days)

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

Interim Health History

Visit 3

Page: 1a of 5

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.	

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:
A	All questions relate to events	s since the previous study visit.	
1)		vents that led to a visit to physician's office/clinient care facility, or a hospitalization?	c/ emergency Yes No
	→If yes, click the "ADD" but	utton and record information for each event	
-	Freatment Location:	Date of Encounter:	
	Physician's Office / Clinic	Day Month Year	
	Emergency Department / Day Hospital / Urgent Car	re Day Month Year	
	Date Admitted: Date Discharged: Day Month Day Day Month Day Day Month Year Day Day Month Year		
Re	Day ason(s) ¹ :	Month Year Day Month Ye	val
	Pain crisis ²	ACS ³ Fever Ac	ute splenic sequestration
	Clinical stroke	Cancer Priapism He	patic sequestration
	Other, specify		
2)	2) Has the subject had any pain crisis(es) at home⁴ for which there was no hospitalization or emergency department/day hospital/urgent care visit? → 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	Select one: units	OR units/cc's unknown
	Reason:		¬
	Exacerbation of anemia due to an aplastic crisis due to splenic sequestration Exacerbation of anemia due to splenic sequestration ACS Other complication of sickle cell disease (CNS event, priapism, AVN)		
	Preparation for anesthesia Other, specify		
² A pa hosp	oital, Emergency Department, clinic, or provide	pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hour ser's office; and is not explained except by sickle cell disease. Sary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, who	

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Comments for page

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⁴ 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</u> <u>not</u> be considered a painful crisis at home.



Comprehensive Sickle Cell Centers	Physical Exam	Visit 3 Page: 1b of 5
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

hysical Exam	
Not Done → Specify:	
1) Weight¹: (kg)	
2) Is the spleen palpable? ☐ Yes² → If yes, what is the current spleen size?	No cm (at the greatest distance below the left costal margin)
3) Did the subject have any new skin lesions? → If yes, where are the lesions located: _	☐ Yes² ☐ No
4) Has subject taken any new medications since → If yes, complete the Concomitant Medication	

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.

 $^{^{\}rm 2}$ If yes, update or add to the AE page as appropriate.

Hematology Labs

Visit 3

Page: 2 of 5

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

НЕМ3

Comprehensive ickle Cell Centers	Hematolog	y Labs	Visit 3 Page: 2 of 5
Hydroxyurea & Magnesium idolate (CHAMPS)			CSCC ID: Center code: Hospital code:
*Cc	ollection Date: Day	Month Year	
☐ Labs not done → Specify:			
TEST	VALU	JE	ELECTROPHORESIS
Hemoglobin (g/dL)		Hb A (%)
Hematocrit (%)			Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit
RBC (x10 ⁶ /mm ³)			Not Done - Suspect Hb A (%) > 10
WBC (x10 ³ /mm ³)			HU/Placebo
MCV (fl)		ANC	Toxicity Check!
MCHC (g/dL)		Plat	elet count < 75 x10³/mm³ ≥ 20% ↓ from Visit 1
Platelet count (x10 ³	/mm³)		al Hb < 5 g/dL or > 13.5 g/dL
% Retic			ither % Retic <u>OR</u> ARC should be provided.
OR ARC (x10 ³ /mm ³)			lse the same unit for this subject at all study visits.

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

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Chemistry Labs

Visit 3

Page: 3 of 5

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 \geq 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

CHE3

Comprehens Sickle Cell Cer		C	Chemistry La	bs		Visit 3		e: 3 of 5	5
Hydroxyurea Magnesiur Pidolate (CHAI	m					CSCC ID:	Center code:		
Was a chemistry → If yes, com → If no, leave	plete this	page.	valuation of toxicity?		Yes	s 🗌	No		
	*Colle	ection Date:	Day Month	/	ear				
TEST		VAL	_UE				/Placebo oxicity Check		
Creatinine (mg/dL)			Not required						

TEST	VA	LUE
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.

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^{*} If the collection date differs from the visit date for this visit, explain: ___

Mg/Placebo Toxicity Check

Visit 3

Page: 4a of 5

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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:dayshours
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 Yes No activities?
→ 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*?
→ If yes, complete an AE Form.
5) What action was taken with Mg/Placebo?
→ If withheld or modified, update the Mg/Placebo Study Drug Dosing Log

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^{*} 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.

Comprehensive Sickle Cell Centers

HU/Placebo
Toxicity Check

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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

Comprehensive Sickle Cell Centers	HU/Placebo Toxicity Check	Visit 3 Page: 4b of 5
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?		
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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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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Pregnancy Test

Visit 3

Page: 5 of 5

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

PREG

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 3 Page: 5 of 5
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

reason below)
le e
not reached menstruating age
ausal
ny
n
ify:
Day Month Year
m Urine
ive Negative

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



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, elec	ctrophoresis is repeated as needed until the subject's Hb %A ≤ 10%.

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

If this visit is also serving as a Toxicity Visit:

- □ Chemistry Panel²
- Chemistry Lab CRF
- 2) Sodium, Potassium, Chloride, CO₂, 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.



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
is the subject taking any medication: List
Please record any other information from this visit for which there is no source document:
Signature Date

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

Visit Four

(Week 4 +/- 4 days)

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

Interim Health History

Visit 4

Page: 1 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 event	s since the previous study visit.	
	events that led to a visit to physician's office/clinic gent care facility, or a hospitalization?	c/ emergency Yes No
→If yes, click the "ADD" b	utton and record information for each event	
Treatment Location:	Date of Encounter:	
Physician's Office / Clinic	Day Month Year	
Emergency Department / Day Hospital / Urgent Ca		
Date	Admitted: Date Discharged:	
Hospital Day	Month Year Day Month Ye	ar
Reason(s) ¹ :		
Pain crisis ²	ACS ³ Fever Acc	ute splenic sequestration
Clinical stroke	Cancer Priapism He	patic sequestration
Other, specify		
	n crisis(es) at home ⁴ for which there was no y department/day hospital/urgent care visit?	Yes No ADD
→ If yes, how many pain cris	ses were treated at home:	
3) Blood Transfusion?	Yes No	
→ If yes, click the "ADD" b	utton and record date and number of units or cc's fo	r each transfusion.
	Select one:	
Date Transfused:/	Month Year Number units cc's	OR units/cc's unknown
Reason:		
Exacerbation of anemia due to an aplastic crisis	Exacerbation of anemia ACS due to splenic sequestration	Other complication of sickle cell disease (CNS event, priapism, AVN)
Preparation for anesthesia	a Other, specify	
hospital, Emergency Department, clinic, or provid	pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours er's office; and is not explained except by sickle cell disease.	

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Comments for page

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⁴ 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</u> <u>not</u> be considered a painful crisis at home.



Comprehensive Sickle Cell Centers	Physical Exam	Visit 4 Page: 2 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

1) Weight ¹ : (kg)			
2) Is the spleen palpable? ☐ Yes² → If yes, what is the current spleen size?	No cm	ance below the le	eft costal margin)
3) Did the subject have any new skin lesions? → If yes, where are the lesions located:	Yes ²	☐ No	

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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.

Hematology Labs

Visit 4

Page: 3 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10. 					

Comprehensive Sickle Cell Centers	Н	lematology Labs		Vis	it 4		l	Page	e: 3 of	f 6
Hydroxyurea & Magnesium idolate (CHAMPS)				CSC			nter co			
*Co	llection Dat	e: Day Month]/	/ear		105p	ilai co	oue.		
Labs not done → Specify:										
TEST		VALUE		ELE	CTR	ROF	МО	RES	is	
Hemoglobin (g/dL)			Н	b A (%)].[
Hematocrit (%)	Hematocrit (%)			tra			ot Done - No recent ansfusion or Hb A (%) 10 at previous visit			
RBC (x10 ⁶ /mm ³)			Not Done - Suspe Hb A (%) > 10							
WBC (x10 ³ /mm ³)				HU/Placebo						
MCV (fl)	MCV (fl)			Toxicity Check! ANC < 1000/mm ³				.!		
MCHC (g/dL)				Platelet count < 75 x10³/mm³ Hb ≥ 20% ↓ from Visit 1				n ³		
Platelet count (x10 ³ /	Platelet count (x10 ³ /mm ³)			Total Hb < 5 g/dL or > 13.5 g/dL				g/dL		
% Retic						pro	vided	l.	nould be	1
OR ARC (x10 ³ /mm ³)				Use the same unit for this sub at all study visits.			subject	t _		
]							

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 4

Page: 4 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 <u>></u> 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

Comprehens Sickle Cell Cer		C	Chemistry La	bs		Visit 4	Pa	ige: 4	of 6
Hydroxyurea Magnesiur Pidolate (CHAI	n					CSCC ID:	Center code		
Was a chemistry → If yes, com → If no, leave	plete this	page.	aluation of toxicity?		Yes	s 🗌	No		
	*Colle	ction Date:	Day Month	/ [ear				
TEST		VAL	.UE				Placebo xicity Chec	ck	
Creatinine (ma/dl.)			Not required						

TEST	VA	LUE
Creatinine (mg/dL)		Not required
SGPT/ALT (U/L)		Not required

SGPT > 2x upper limit of normal

HU/Placebo Renal Toxicity Check

Creatinine \geq 1.2 mg/dL subjects < 18 years of age Creatinine \geq 1.4 mg/dL subjects \geq 18 years of age

If toxicity occurs, <u>stop</u> the study drug associated with the toxicity.

^{*} If the collection date differs from the visit date for this visit, explain: ______

Mg/Placebo Toxicity Check

Visit 4

Page: 5a of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 c	ode:		
		ŀ	Hospital co	ode:		

All questions relate to events since the previous visit.

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:dayshours
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 Yes No activities?
→ 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?
→ 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.

HU/Placebo Toxicity Check

Visit 4

Page: 5b of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 4	Page: 5b of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Cent	er code:
i ideidie (Grinami e)		Hospit	al 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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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

Pregnancy Test

Visit 4

Page: 6 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 4 Page: 6 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Subject ma	ale	
Subject ha	s not reached menstruating age	
Postmenor	pausal	
Hysterecto	my	
Tubal ligati	on	
Other, spe	sify:	
ate of Collection:	Day Month Year	
Type: Seri	um Urine	
Result: Pos	itive Negative	

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



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
۵	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	t 6 to CHAMPS_labs@rhoworld.com.
		lectrophoresis is repeated as needed until the subject's Hb %A ≤ 10%. 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

If this visit is also serving as a Toxicity Visit:

- Chemistry Panel²
- Chemistry Lab CRF
- 2) Sodium, Potassium, Chloride, CO2, 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.

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).



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
is the subject taking any medication: List
Please record any other information from this visit for which there is no source document:
Signature Date

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

Visit Five

(Week 6 +/- 4 days)

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

Interim Health History

Visit 5

Page: 1 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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: / / / /	CSCC ID:	Center code:	
	Expected Date of Next Visit:	Day Month Year Day Month Year → Email dat		ospital code: S_labs@rhoworld.co	om
	Has the subject had acute of department/day hospital/urg	since the previous study visit. Events that led to a visit to physician's office/clinical lent care facility, or a hospitalization? Utton and record information for each event	c/ emergend	cy	
-	Freatment Location: Physician's Office / Clinic	Date of Encounter: Day Month Year			
	Emergency Department / Day Hospital / Urgent Ca	re//			
Re	Hospital Day Pason(s) ¹ :	Admitted: Date Discharged: Month Year Day Month Year Year Day Month Year Day Day Month Year Day Month Month Year Day Month M	ear		
	Pain crisis² Clinical stroke Other, specify		cute splenic s	·	
2)		n crisis(es) at home ⁴ for which there was no y department/day hospital/urgent care visit?	Y	es No	ADD
3)	Blood Transfusion? → If yes, click the "ADD" b	Yes No utton and record date and number of units or cc's fo Select one:	or each transf	usion.	
	Date Transfused: Day	Month Year Number Cc's	OR	units/cc's unknown	
	Reason: Exacerbation of anemia due to an aplastic crisis Preparation for anesthesia	Exacerbation of anemia due to splenic sequestration Other, specify		mplication of sickle co	
² A pa		pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hour; and is not explained except by sickle cell disease.	s; requires a visit to	a hospital,	ADD
3 Acut	e chest syndrome is defined as a new pulmor	ary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, who a steady state situation. A pain crisis at home is defined as the occurrence of p			

⁴ 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.



Comprehensive Sickle Cell Centers	Physical Exam	Visit 5 Page: 2 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

1) Weight ¹ : (kg)			
2) Is the spleen palpable? ☐ Yes² → If yes, what is the current spleen size?	No cm	ance below the le	eft costal margin)
3) Did the subject have any new skin lesions? → If yes, where are the lesions located:	Yes ²	☐ No	

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.

Hematology Labs

Visit 5

Page: 3 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	n 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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

Comprehensive Sickle Cell Centers	He	ematology Labs	;	Visi	t 5	Page	e: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)				cscc	Cen	ter code:	
	llection Date	: Day Month]/	ar	ноѕрг	tal code:	
☐ Labs not done → Specify:					_		
TEST		VALUE		ELEC	CTROP	HORES	SIS
Hemoglobin (g/dL)			Hb	A (%)		-	
Hematocrit (%)					trar	t Done - N nsfusion o 0 at previ	r Hb A (%
RBC (x10 ⁶ /mm ³)						t Done - S A (%) > 1	
WBC (x10 ³ /mm ³)				· ·	HU/PI	acebo	
MCV (fl)				ANC < 100		/ Check	:!
MCHC (g/dL)		<u>.</u> .		Platelet co		5 x10³/mn ′isit 1	n ³
Platelet count (x10 ³ /r	mm³)			Γotal Hb ⊲	< 5 g/dL o	or > 13.5 (g/dL
% Retic			 		prov	PR ARC should also should be a second and a second also should be a second also should be a second and a second also should be a second and a second also should be a second and a second a	
ARC (x10 ³ /mm ³)				OSE ITE		idy visits.	Subject
ANC (x10 ³ /mm ³)							
e collection date differs from th	ne visit date fo	or this visit, explain:					

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 5

Page: 4 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 \geq 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

CHE3

Comprehens Sickle Cell Cer		C	Chemistry La	abs		Visit 5	Pag	e: 4 of (6
Hydroxyurea Magnesiur Pidolate (CHAI	m					CSCC ID:	Center code:		
Was a chemistry → If yes, com → If no, leave	plete this	page.	valuation of toxicity	? [Yes		No		
	*Collec	ction Date:	Day Month	/	ear				
TEST		VAL	.UE				Placebo exicity Check	(
Creatinine (mg/dL)].[]	Not required						

. 20 .	• 7 (1	
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: ___

Mg/Placebo Toxicity Check

Visit 5

Page: 5a of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.	

Comprehensi		Mg/Placebo Toxicity Chec	k	Visit 5	Page: 5a of 6	
Giorie dell'ochi	.073			CSCC ID:		
Hydroxyurea				CSCC ID.		
Magnesium Pidolate (CHAM				Cei	nter code:	
,				Hosp	oital code:	
All questions relate t	o events since the pr	revious visit.				
1) Since the last visit (diarrhea has/is:	Diarrhea was not	evaluated at this vis	it		
Resolved	Ongoing Worsen	ned New	Not present at the previous visit	his visit and was	not present at the	
→ If new, ongo	ing, or worsened:		•			
Grade:	<u> </u>	☐ 4 → See CF	RF Completion Gu	idelines for gra	nding criteria.	
→ Fo.	r all Grades complete	AE form				
→ Fo.	r Grade 3 complete SA	AE form if subject is i	hospitalized			
→ Fo.	r Grade 4 complete SA	AE form				
Duration:	days	hours				
2) Since the last visit	2) Since the last visit abdominal pain has/is: Abdominal pain was not evaluated at this visit					
Resolved	Resolved Ongoing Worsened New Not present at this visit and was not present at the previous visit					
→ If ongoing, w activities?	→ If ongoing, worsened, or new, is pain severe enough to interfere with daily Yes No activities?					
→ If resolve	→ If resolved or ongoing modify AE Form as appropriate					
→ If new , ac	ld AE to AE Form					
3) Since last visit sigr	ns of dehydration hav	re/are? D	ehydration was no	t evaluated at	this visit	
Resolved	Ongoing Worse	ened New	Not present at previous visit	this visit and wa	as not present at the	
→ If resolved or	ongoing modify AE F	orm as appropriate	·			
→ If new , add Al	to AE Form					
4) Does/did subject m	eet criteria for Mg/Pla	acebo toxicity*?	Yes	☐ No		
→ If yes, complete	e an AE Form.		·			
5) What action was tal	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.

HU/Placebo Toxicity Check

Visit 5

Page: 5b of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 5	Page: 5b of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID:	Center code:
		Н	lospital code:

All questions relate to events since the previous visit.

All questions relate to events since the previous visit.		
HU/Placebo Hepatic Toxicity Check		
SGPT > 2x upper limit of normal		
1) Hepatic toxicity?		
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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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		

Pregnancy Test

Visit 5

Page: 6 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 5 Page: 6 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Prognancy Tost
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

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



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 				
	Hold off on labs until the next visit IF subject has been:				
	 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

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



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
is the subject taking any medication: List
Please record any other information from this visit for which there is no source document:
Signature Date



RhoLAB Specimen ID Tracker January 4, 2007

Subject ID Number _____ Visit Date _____ 10-mL lavender vacutainer Place here 10-mL lavender vacutainer Place here 5-mL green vacutainer Place here 5-mL lavender vacutainer

Place

here



CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

Visit Six

(Week 8 +/- 4 days)

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

Interim Health History

Visit 6

Page: 1 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.

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 <u>acute events</u> that led to a visit to physician's office/clinic/ emergency Yes No department/day hospital/urgent care facility, or a hospitalization?							
→If yes, click the "ADD" b	utton 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 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	Clinical stroke Cancer Priapism Hepatic sequestration						
Other, specify							
2) Has the subject had any <u>pain crisis(es) at home</u> for which there was no hospitalization or emergency department/day hospital/urgent care visit?							
→ If yes, how many pain cris	ses were treated at home:						
3) Blood Transfusion?	Yes No						
→ If yes, click the "ADD" b	utton and record date and number of units or cc's fo	r each transfusion.					
Date Transfused: Day	Select one: Month Year Number Cc's	OR units/cc's unknown					
Reason:							
Exacerbation of anemia due to an aplastic crisis Exacerbation of anemia due to an aplastic crisis Exacerbation of anemia disease (CNS event, priapism, AVN)							
Preparation for anesthesia Other, specify							
¹ Complete AE and/or SAE forms for each reason.		ADD					
hospital, Emergency Department, clinic, or provid	pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours ar's office; and is not explained except by sickle cell disease. hary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, who						

Comments for page

⁴ 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.



Comprehensive Sickle Cell Centers	Physical Exam	Visit 6 Page: 2 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

1) Weight ¹ : (kg)			
2) Is the spleen palpable? ☐ Yes² → If yes, what is the current spleen size?	No cm	ance below the le	eft costal margin)
3) Did the subject have any new skin lesions? → If yes, where are the lesions located:	Yes ²	☐ No	

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.

Hematology Labs

Visit 6

Page: 3 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

Comprehensive Sickle Cell Centers	Н	ematology Labs		Visit	6 Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)				CSCC II	Center code: Hospital code:
☐ Labs not done		Day Month]/		_
TEST		VALUE		ELEC.	TROPHORESIS
Hemoglobin (g/dL)			Hb	A (%)	
Hematocrit (%)					Not Done - No recent transfusion or Hb A (% ≤ 10 at previous visit
RBC (x10 ⁶ /mm ³)					Not Done - Suspect Hb A (%) > 10
WBC (x10 ³ /mm ³)					HU/Placebo
MCV (fl)				To	oxicity Check!
MCHC (g/dL)			P		o/mm³ u nt < 75 x10³/mm³ from Visit 1
Platelet count (x10 ³ /	/mm³)				5 g/dL or > 13.5 g/dL
% Retic OR ARC (x10³/mm³)	-		 	Use the s	Retic <u>OR</u> ARC should be provided. same unit for this subject at all study visits.
			1		

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 6

Page: 4 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.	

Comprehensive Sickle Cell Centers	Chemistry L	abs Visit 6	Page: 4 of 6		
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC IE	Center code: Hospital code:		
*C ☐ Labs not done → Specify:	collection Date: Day	Month Year	_		
TEST	VALUE				
Sodium (mmol/L)		HU	/Placebo		
Potassium (mmol/L)		Renal Toxicity Check			
Chloride (mmol/L)		SGPT > 2x upper limit of normal			
CO ₂ (mmol/L)			/Placebo		
BUN (mg/dL)		Renal Toxicity Check			
Creatinine (mg/dL)		Creatinine ≥ 1.2 mg/dL subjects < 18 years of age Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age			
Calcium (mg/dL)					
SGPT/ALT (U/L)					
Alk phosphatase (U/L)		If toxicity occurs, stop the studrug associated with the			
Total bilirubin (mg/dL)			kicity.		
Total protein (g/dL)					
Albumin (g/dL)					
LDH (U/L)					

^{*} If the collection date differs from the visit date for this visit, explain: ______.

Mg/Placebo Toxicity Check

Visit 6

Page: 5a of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	Mg/Placebo Toxicity Check	Visit 6 Page: 5a of 6			
Sickle Cell Centers	TOXICITY CHECK				
I hadraaaaa o		CSCC ID:			
Hydroxyurea & Magnesium			Center of	code:	
Pidolate (CHAMPS)				_	
		-	lospital c	ode:	
All questions relate to ever	nts since the previous visit.	•			
1) Since the last visit diarrhe	ea has/is: Diarrhea was not evaluated at this v	isit			
Resolved Ongoing	Worsened New Not present at previous visit	this visit and	was not	present at	the
→ If new, ongoing, or	·				
Grade: 1	☐ 2 ☐ 3 ☐ 4 → See CRF Completion G	uidelines for	grading	g criteria.	
→ For all Gr	rades complete AE form				
→ For Grad	e 3 complete SAE form if subject is hospitalized				
→ For Grad	e 4 complete SAE form				
Duration:	_dayshours				
2) Since the last visit abdom	ninal pain has/is: Abdominal pain was not	evaluated a	nt this vi	sit	
Resolved Ongoir	ng Worsened New Not present a previous visit	at this visit and	d was no	t present a	at the
→ If ongoing, worsene activities?	ed, or new, is pain severe enough to interfere with da	aily Ye	s [No	
→ If resolved or or	ngoing modify AE Form as appropriate				
\rightarrow If new , add AE to	o AE Form				
3) Since last visit signs of d	ehydration have/are? Dehydration was r	not evaluated	d at this	visit	
Resolved Ongoi	ng Worsened New Not present previous visi	at this visit an t	d was no	ot present	at the
→ If resolved or ongo.	ing modify AE Form as appropriate				
\rightarrow If new, add AE to AE	Form				
4) Does/did subject meet cri	teria for Mg/Placebo toxicity*?	☐ No			
→ If yes, complete an AE Form.					
5) What action was taken wit	th Mg/Placebo? No change Withhe	eld N	Modified		
→ If withheld or modified	d , 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.

HU/Placebo Toxicity Check

Visit 6

Page: 5b of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	Pa	ige: 5	5b of	f 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID:	Center code) e: [
		ŀ	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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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

Pregnancy Test

Visit 6

Page: 6 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 6 Page: 6 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

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	



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	t 8 to CHAMPS_labs@rhoworld.com.
	fused, electrophoresis is repeated as needed until the subject's Hb %A should come in for another test prior to Visit 8 for another

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

If this visit is also serving as a Toxicity Visit:

- □ Chemistry Panel²
- □ Chemistry Lab CRF
- 2) Sodium, Potassium, Chloride, CO₂, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH



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
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

Interim Health History

Visit 7

Page: 1 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	e to CHAMPS_labs@rhoworld.com
1) Has the subject had <u>acute</u> department/day hospital/urg	since the previous study visit. events that led to a visit to physician's office/clinic gent care facility, or a hospitalization? outton and record information for each event	c/ emergency Yes No
	dution and record information for each event	
Treatment Location: Physician's Office / Clinic	Date of Encounter: Day Month Year	
Emergency Department Day Hospital / Urgent Ca		
Date Hospital Day Reason(s)¹:	Admitted: Date Discharged: Month Day Month Year Day Month Year	ar
Pain crisis ²	ACS ³ Fever Ac	ute splenic sequestration
Clinical stroke Other, specify	Cancer Priapism He	patic sequestration
	in crisis(es) at home ⁴ for which there was no cy department/day hospital/urgent care visit?	Yes No ADD
3) Blood Transfusion?→ If yes, click the "ADD" b	Yes No putton and record date and number of units or cc's for	r each transfusion.
Date Transfused:/	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	Other complication of sickle cell disease (CNS event, priapism, AVN)
Preparation for anesthesia	Other, specify	
Emergency Department, clinic, or provider's office	pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours at least 2 hours are in the explained except by sickle cell disease.	s; requires a visit to a hospital,

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 <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.

Comprehensive Sickle Cell Centers	Interim Health History	Visit 7 Page: 2 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
Laucationa relata ta aventa sin		Hospital code:

Il questions relate to	events since Visit	t 2.				
cer						
e Visit 2, has this	subject been diag	gnosed with cancer?		Yes	☐ No	
If yes, record deta	ils below and com	plete Adverse Event a	and Serious Adver	rse Event forn	ns as appropri	ate.
Date diagnosed:	Day N	/ Year	Type: Location:			
						Al
roimaging						
If yes, click the AE	DD button and reco	ne any neuroimaging			Yes] No
 If yes, click the AL → Complete one Date of test¹: 	DD button and record for each ty	ord details for each typope of test.			Yes] No
 If yes, click the AL → Complete one Date of test¹: 	DD button and reco	ord details for each typ		ohy C	Yes	
→ Complete one Date of test¹: Type of test: (check one) Was this result	DD button and record for each ty /	ord details for each typope of test.	Cerebral angiograp	hy		

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

Comprehensive Sickle Cell Centers	Physical Exam	Visit 7 Page: 3 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

hysic	cal Exam
[Not Done → Specify:
1	I) Weight¹: (kg)
2	2) Is the spleen palpable? ☐ Yes² ☐ No → If yes, what is the current spleen size? cm (at the greatest distance below the left costal margin)
3	3) Did the subject have any new skin lesions?
4	I) Has subject taken any new medications since previous visit? ☐ Yes ☐ No → If yes, complete the Concomitant Medications page:

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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.

 $^{^{\}rm 2}$ If yes, update or add to the AE page as appropriate.

Hematology Labs

Visit 7

Page: 4 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

Comprehensive Sickle Cell Centers	Hematolog	gy Labs	Visit 7	Page: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)			CSCC ID:	Center code:
*Col	lection Date: Day	//	Year	Hospital code:
☐ Labs not done → Specify:				
TEST	VAL	UE	ELECTF	ROPHORESIS
Hemoglobin (g/dL)		. 🗆 📄	Hb A (%)	□.□
Hematocrit (%)				Not Done - No recent transfusion or Hb A (% ≤ 10 at previous visit
RBC (x10 ⁶ /mm ³)				Not Done - Suspect Hb A (%) > 10
WBC (x10 ³ /mm ³)			H	U/Placebo
MCV (fl)		. 🗆 📗	ANC < 1000/n	icity Check!
MCHC (g/dL)		. 🗆		t < 75 x10 ³ /mm ³
Platelet count (x10 ³ /r	mm³)			g/dL or > 13.5 g/dL
% Retic		. 🗆	Use the sai	etic <u>OR</u> ARC should be provided. me unit for this subject
ARC (x10 ³ /mm ³)			at a	all study visits.
ANC (x10 ³ /mm ³)				

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 7

Page: 5 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.

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Comprehens Sickle Cell Cer		C	Chemistry Lab	os		Visit 7	Page	e: 5 of	7
Hydroxyurea Magnesiur Pidolate (CHAI	m					CSCC ID:	Center code:		
Was a chemistry → If yes, com → If no, leave	plete this	page.	valuation of toxicity?		Yes	s 🗌	No		
	*Colle	ection Date:	Day Month]/ [_Y	ear				
TEST		VAL	LUE				Placebo exicity Check		
Creatinine (mg/dL)			Not required		SGPT		r limit of norm	al	ĺ

Not required

SGPT/ALT (U/L)

HU/Placebo
Renal Toxicity Check

Creatinine \geq 1.2 mg/dL subjects < 18 years of age Creatinine \geq 1.4 mg/dL subjects \geq 18 years of age

If toxicity occurs, <u>stop</u> the study drug associated with the toxicity.

^{*} If the collection date differs from the visit date for this visit, explain: _____

Mg/Placebo Toxicity Check

Visit 7

Page: 6a of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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		
Lludray, grass 9		CSCC ID:		
Hydroxyurea & Magnesium		Center code:		
Pidolate (CHAMPS)				
		Hospital code:		
All questions relate to even	<u> </u>			
1) Since the last visit diarrhe	a has/is: Diarrhea was not evaluated at this vis	sit		
Resolved Ongoing	Worsened New Not present at to previous visit	his visit and was not present at the		
→ If new, ongoing, or	worsened:			
Grade: 1	2 ☐ 3 ☐ 4 → See CRF Completion Gu	idelines for grading criteria.		
→ For all Gr a	ades complete AE form			
→ For Grade	3 complete SAE form if subject is hospitalized			
→ For Grade	• 4 complete SAE form			
Duration:	_dayshours			
2) Since the last visit abdom	inal pain has/is: Abdominal pain was not	evaluated at this visit		
Resolved Ongoin	g Worsened New Not present at previous visit	this visit and was not present at the		
→ If ongoing, worsened, or new, is pain severe enough to interfere with daily Yes No activities?				
→ If resolved or on	going modify AE Form as appropriate			
→ If new , add AE to	→ 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 crit	teria for Mg/Placebo toxicity*?	No		
→ If yes, complete an AE	Form.			
5) What action was taken with Mg/Placebo?				
→ 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.

HU/Placebo Toxicity Check

Visit 7

Page: 6b of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.	

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Comprehensive Sickle Cell Centers	HU/Placebo Toxicity Check	Visit 7 Page: 6b of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

All questions relate to events since the previous visit.

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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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		

Pregnancy Test

Visit 7

Page: 7 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 7 Page: 7 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Subject male			
Subject has not read	ched menstruating age		
Postmenopausal			
Hysterectomy			
Tubal ligation			
Other, specify:			
ate of Collection: Day	///		
Type: Serum [Urine		
Result: Positive [Negative		

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



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
	Hold off on labs until the next visit IF subject has been:
	 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



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
is the subject taking any medication: List
Please record any other information from this visit for which there is no source document:
Signature Date



RhoLAB Specimen ID Tracker January 4, 2007

Subject ID Number _____ Visit Date _____ 10-mL lavender vacutainer Place here 10-mL lavender vacutainer Place here 5-mL green vacutainer Place here 5-mL lavender vacutainer

Place

here



Visit Eight

(Month 4 +/- 8 days)

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

Interim Health History

Visit 8

Page: 1 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 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:
	Has the subject had <u>acute e</u>	s since the previous study visit.	c/ emergency Yes No
		ent care facility, or a hospitalization? utton and record information for each event	
-	Freatment Location:	Date of Encounter:	
'	Physician's Office / Clinic	Day Month Year	
	Emergency Department / Day Hospital / Urgent Car	re Day / Month / Year	
Re	Date Hospital Day ason(s)¹:	Admitted: Date Discharged: /	ar
	Pain crisis²	ACS ³ Fever Acc	ute splenic sequestration
	Clinical stroke Other, specify	Cancer Priapism He	patic sequestration
		n crisis(es) at home ⁴ for which there was no y department/day hospital/urgent care visit?	Yes No ADD
	→ If yes, how many pain cris	es were treated at home:	
3)	Blood Transfusion?	Yes No	
	→ If yes, click the "ADD" b	utton and record date and number of units or cc's for	r each transfusion.
	Date Transfused: Day	Select one: Units Number Cc's	OR units/cc's unknown
	Reason: Exacerbation of anemia due to an aplastic crisis Preparation for anesthesia	Exacerbation of anemia ACS [due to splenic sequestration	Other complication of sickle cell disease (CNS event, priapism, AVN)
² A pa hosp	oital, Emergency Department, clinic, or provide	pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours or's office; and is not explained except by sickle cell disease. ary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, whe	•

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.



Comprehensive Sickle Cell Centers	Physical Exam	Visit 8 Page: 2 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Not Done → Specify: 1) Weight¹: (kg)			
	□ N:		
2) Is the spleen palpable? Yes² → If yes, what is the current spleen size?	No cm	tance below the le	eft costal margin)
3) Did the subject have any new skin lesions? → If yes, where are the lesions located:	Yes ²	☐ No	
4) Has subject taken any new medications since → If yes, complete the Concomitant Medication		Yes	☐ No

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.

Hematology Labs

Visit 8

Page: 3 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10. 			

Comprehensive Sickle Cell Centers	F	lematology Labs		Visit	8 Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)				CSCCI	Center code: Hospital code:
*Co	ollection Dat	te: /	/		i iospitai code.
☐ Labs not done → Specify:		Day Month	Yea	r 	
TEST		VALUE		ELEC	TROPHORESIS
Hemoglobin (g/dL)			Hb /	A (%)	
Hematocrit (%)					Not Done - No recent transfusion or Hb A (% ≤ 10 at previous visit
RBC (x10 ⁶ /mm ³)					Not Done - Suspect Hb A (%) > 10
WBC (x10 ³ /mm ³)					HU/Placebo
MCV (fl)				NC < 1000	oxicity Check!
MCHC (g/dL)			P	latelet co	unt < 75 x10 ³ /mm ³ From Visit 1
Platelet count (x103	/mm³)				5 g/dL or > 13.5 g/dL
% Retic OR ARC (x10 ³ /mm ³)			→ [Use the	Retic <u>OR</u> ARC should be provided. same unit for this subject at all study visits.
ARC (x10-/IIIII1-)					

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 8

Page: 4 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.			

Comprehensive Sickle Cell Centers	Chemistry L	.abs Vis	it 8 Page: 4 of 6		
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSC	C ID: Center code: Hospital code:		
*C Labs not done → Specify:	Collection Date: Day	Month Year			
TEST	VALUE				
Sodium (mmol/L)			HU/Placebo		
Potassium (mmol/L)		Renal Toxicity Check			
Chloride (mmol/L)		SGPT > 2x upper limit of normal			
CO ₂ (mmol/L)			HU/Placebo		
BUN (mg/dL)		Renal Toxicity Check			
Creatinine (mg/dL)		Creatinine ≥ 1.2 mg/dL subjects < 18 years of ago Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of ago			
Calcium (mg/dL)					
SGPT/ALT (U/L)					
Alk phosphatase (U/L)		If toxicity occurs, stop the study drug associated with the toxicity.			
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: ______.

Mg/Placebo Toxicity Check

Visit 8

Page: 5a of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 ever	nts <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	•			
Grade: 1	☐ 2 ☐ 3 ☐ 4 → See CRF Completion Gu	idelines for grading	g criteria.	
→ For all Gr	ades complete AE form			
→ For Grade 3 complete SAE form if subject is hospitalized				
→ For Grade	• 4 complete SAE form			
Duration:	_dayshours			
2) Since the last visit abdom	inal pain has/is: Abdominal pain was not	evaluated at this vi	sit	
Resolved Ongoin	g Worsened New Not present a previous visit	t this visit and was no	t present at the	
→ If ongoing, worsened, or new, is pain severe enough to interfere with daily Yes No activities?				
→ If resolved or on	going 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 Ongoin	ng Worsened New Not present a previous visit	t this visit and was no	ot present at the	
→ If resolved or ongoing modify AE Form as appropriate				
\rightarrow If new, add AE to AE	Form			
4) Does/did subject meet crit	teria for Mg/Placebo toxicity*?	No No		
→ If yes, complete an AE	Form.			
5) What action was taken with Mg/Placebo? No change Withheld Modified				
→ If withheld or modified	d, 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.

HU/Placebo Toxicity Check

Visit 8

Page: 5b of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 &		CSCC ID:	
Magnesium Pidolate (CHAMPS)		Center of	code:
		Hospital c	ode:

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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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				

Pregnancy Test

Visit 8

Page: 6 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 8 Page: 6 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Programmy Took
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: _____



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 Visi	t 10 to CHAMPS_labs@rhoworld.com.
	lectrophoresis is repeated as needed until the subject's Hb %A ≤ 10%. 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

If this visit is also serving as a Toxicity Visit:

- □ Chemistry Panel²
- □ Chemistry Lab CRF
- 2) Sodium, Potassium, Chloride, CO₂, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH



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
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

Interim Health History

Visit 9

Page: 1 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	s since the previous study visit.	-
	events that led to a visit to physician's office/clinic pent care facility, or a hospitalization?	c/ emergency Yes No
→If yes, click the "ADD" b	utton and record information for each event	
Treatment Location:	Date of Encounter:	
Physician's Office / Clinic	Day Month Year	
Emergency Department / Day Hospital / Urgent Ca		
Date Hospital Day	Admitted: Date Discharged: January Januar	ar
Reason(s)¹:		ai
Pain crisis ²	ACS ³ Fever Ac	ute splenic sequestration
Clinical stroke	Cancer Priapism He	patic sequestration
Other, specify		
	n crisis(es) at home ⁴ for which there was no y department/day hospital/urgent care visit?	Yes No ADD
→ If yes, how many pain cris	ses were treated at home:	
3) Blood Transfusion?	Yes No	
→ If yes, click the "ADD" b	utton and record date and number of units or cc's for	r each transfusion.
Date Transfused: Day	Select one: Units Cc's	OR units/cc's unknown
Reason: Exacerbation of anemia due to an aplastic crisis	Exacerbation of anemia ACS [due to splenic sequestration	Other complication of sickle cell disease (CNS event, priapism, AVN)
Preparation for anesthesia	Other, specify	
Emergency Department, clinic, or provider's office	pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours e; and is not explained except by sickle cell disease. hary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, whe	

Comments for page

⁴ 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.



Comprehensive Sickle Cell Centers	Physical Exam	Visit 9 Page: 2 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

1) Weight ¹ : (kg)			
2) Is the spleen palpable? ☐ Yes² → If yes, what is the current spleen size?	No cm	ance below the le	eft costal margin)
3) Did the subject have any new skin lesions? → If yes, where are the lesions located:	Yes ²	☐ No	

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.

 $^{^{\}rm 2}$ If yes, update or add to the AE page as appropriate.

Hematology Labs

Visit 9

Page: 3 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

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Comprehensive Sickle Cell Centers	Н	ematology Labs	6	Visit 9		Page	: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)				CSCC ID	Center c		
*Co	llection Date	p:/]/ 🔲		Hospital c	ode:	
☐ Labs not done → Specify:		Day Month	Yea	ar	_		
TEST		VALUE		ELECT	ROPHO	RESI	IS
Hemoglobin (g/dL)			Hb	A (%)	<u></u> .[
Hematocrit (%)					transfu	sion or	recent Hb A (% ous visit
RBC (x10 ⁶ /mm ³)					Not Do Hb A (9		
WBC (x10 ³ /mm ³)		-			IU/Place		
MCV (fl)			_	Toxicity Check! ANC < 1000/mm ³		!	
MCHC (g/dL)				latelet cou lb ≥ 20% ↓			3
Platelet count (x10 ³ /	/mm³)		Т	otal Hb < 5	g/dL or >	13.5 g	/dL
% Retic OR ARC (x10 ³ /mm ³)	_		-	Either % R Use the sa	provided	d. or this	
, , ,			1				

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 9

Page: 4 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 \geq 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

Comprehens Sickle Cell Cer		C	Chemistry La	bs		Visit 9	Pa	ige: 4 d	of 6
Hydroxyurea Magnesiur Pidolate (CHAI	n					CSCC ID:	Center code		
Was a chemistry → If yes, com → If no, leave	plete this	page.	valuation of toxicity?		Yes	s	No		
	*Colle	ection Date:	Day Month	/	ear				
TEST		VAL	_UE				Placebo exicity Chec	ck	
Creatinine (mg/dL)		\neg	Not required						

TEST	VA	LUE
Creatinine (mg/dL)		Not required
SGPT/ALT (U/L)		Not required

HU/Placebo Renal Toxicity Check	
DT . Ou company limit of manuscal	

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.

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^{*} If the collection date differs from the visit date for this visit, explain: _

Mg/Placebo Toxicity Check

Visit 9

Page: 5a of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 persists for more than 72 hours OR if there are signs of dehydration from if the subject has abdominal pain severe enough to interfere with daily a		

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 even	<u> </u>	
1) Since the last visit diarrhe	a has/is: Diarrhea was not evaluated at this vis	sit
Resolved Ongoing	Worsened New Not present at the previous visit	his visit and was not present at the
→ If new, ongoing, or	·	
Grade: 1	2	idelines for grading criteria.
→ For all Gr a	ades complete AE form	
	3 complete SAE form if subject is hospitalized	
→ For Grade	• 4 complete SAE form	
Duration:	_dayshours	
2) Since the last visit abdom	inal 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 Yes No activities?		
→ If resolved or on	going modify AE Form as appropriate	
→ If new , add AE to	AE Form	
3) Since last visit signs of de	ehydration have/are? Dehydration was no	ot evaluated at this visit
Resolved Ongoir	ng Worsened New Not present a previous visit	t this visit and was not present at the
→ If resolved or ongoing	ng modify AE Form as appropriate	
→ If new, add AE to AE	Form	
4) Does/did subject meet crit	eria for Mg/Placebo toxicity*?	No
→ If yes, complete an AE	Form.	
5) What action was taken wit	h Mg/Placebo? No change Withhe	ld Modified
→ If withheld or modified	I, 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.

HU/Placebo Toxicity Check

Visit 9

Page: 5b of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.

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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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

Pregnancy Test

Visit 9

Page: 6 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 9 Page: 6 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

	Not Done (Check reason below)
	Subject male
	Subject has not reached menstruating age
	Postmenopausal
	Hysterectomy
	Tubal ligation
	Other, specify:
*Da	te of Collection: Day Month Year
	Type: Serum Urine
	Result: Positive Negative

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



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 Hold off on labs until the next visit IF subject has been: 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



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
is the subject taking any medication: List
Please record any other information from this visit for which there is no source document:
Signature Date



RhoLAB Specimen ID Tracker January 4, 2007

Subject ID Number _____ Visit Date _____ 10-mL lavender vacutainer Place here 10-mL lavender vacutainer Place here 5-mL green vacutainer Place here 5-mL lavender vacutainer

Place

here



Visit Ten

(Month 6 +/- 8 days)

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

Interim Health History

Visit 10

Page: 1 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 Yes No department/day hospital/urgent care facility, or a hospitalization? →If yes, click the "ADD" button and record information for each event							
-	Physician's Office / Clinic Emergency Department / Day Hospital / Urgent Car	Day Month Year						
Re	Date Hospital Day ason(s)¹: Pain crisis² Clinical stroke Other, specify		ar ute splenic sequestration patic sequestration					
	hospitalization or emergency → If yes, how many pain crise Blood Transfusion?	n crisis(es) at home ⁴ for which there was no y department/day hospital/urgent care visit? es were treated at home: Yes No utton and record date and number of units or cc's for	Yes No ADD					
	Date Transfused: Day	Select one: Units Cc's Cc's	OR units/cc's unknown					
¹ Com	Reason: Exacerbation of anemia due to an aplastic crisis Preparation for anesthesia	Exacerbation of anemia ACS due to splenic sequestration Other, specify	Other complication of sickle cell disease (CNS event, priapism, AVN)					
² A pa Eme	in crisis is defined here as the occurrence of pregency Department, clinic, or provider's office	nain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; and is not explained except by sickle cell disease.						

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⁴ 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.

Comprehensive Sickle Cell Centers	Interim Health History	Visit 10 Page: 2 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Vicit 7, has this s	ubject been diagnosed wit	h cancar?		¬		
	s below and complete Adver		ious Adverse	Yes e Event form	No ns as appropri	riate.
Date diagnosed:	Day Month		rpe:			
oimaging						
	uhioot undorgono any nou	roimoging proce	odurac?			٦.,
Visit 7, has this s	ubject undergone any neu				Yes	No
Visit 7, has this s	ubject undergone any neu D button and record details fecord for each type of test.				Yes] No
Visit 7, has this s If yes, click the ADE → Complete one r	D button and record details feecord for each type of test.				Yes] No
Visit 7, has this s f yes, click the ADE → Complete one r Date of test: Da Type of test¹:	D button and record details feecord for each type of test.			,	Yes	No
Visit 7, has this s f yes, click the ADE → Complete one r Date of test: Da Type of test¹:	button and record details for each type of test.	or each type of tes	st. Cerebral	,		No No
Visit 7, has this solid yes, click the ADE → Complete one roll Date of test: Type of test¹: (check one)	button and record details frecord for each type of test.	or each type of tes	st. Cerebral angiography	, "		No No

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

Comprehensive Sickle Cell Centers	Physical Exam	Visit 10 Page: 3 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

1) Weight ¹ : (kg)			
2) Is the spleen palpable? ☐ Yes² → If yes, what is the current spleen size?	No cm	ance below the le	eft costal margin)
3) Did the subject have any new skin lesions? → If yes, where are the lesions located:	Yes ²	☐ No	

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.

Hematology Labs

Visit 10

Page: 4 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

Comprehensive Sickle Cell Centers	Н	ematology Labs		Visit 10	Page: 4 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)					nter code:
*Co	llection Date	L/]/ 🔲		ital code:
☐ Labs not done → Specify:		Day Month	Yea	.r	
TEST		VALUE		ELECTROP	PHORESIS
Hemoglobin (g/dL)			Hb.	A (%)]. 🗌
Hematocrit (%)				tra	t Done - No recent nsfusion or Hb A (% I0 at previous visit
RBC (x10 ⁶ /mm ³)					ot Done - Suspect A (%) > 10
WBC (x10 ³ /mm ³)				HU/P	lacebo
MCV (fl)				Toxicity	y Check!
MCHC (g/dL)			P	latelet count < 7 $ \mathbf{b} \ge 20\% \downarrow \text{ from } \setminus$	
Platelet count (x10 ³	/mm³)			otal Hb < 5 g/dL	
% Retic OR ARC (x10 ³ /mm ³)			→ [prov Use the same u	DR ARC should be vided. unit for this subject udy visits.
			_		

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 10

Page: 5 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.

Comprehensive Sickle Cell Centers Hydroxyurea & Magnesium Pidolate (CHAMPS)	Chemistry L	Page: 5 of 8 CSCC ID: Center code: Hospital code:			
*Collection Date: Day Month Year Labs not done → Specify:					
TEST	VALUE				
Sodium (mmol/L)		HU/Placebo			
Potassium (mmol/L)		Renal Toxicity Check			
Chloride (mmol/L)		SGPT > 2x upper limit of normal			
CO ₂ (mmol/L)		HU/Placebo			
BUN (mg/dL)		Renal Toxicity Check			
Creatinine (mg/dL)		Creatinine ≥ 1.2 mg/dL subjects < 18 years of age Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age			
Calcium (mg/dL)					
SGPT/ALT (U/L)					
Alk phosphatase (U/L)		If toxicity occurs, <u>stop</u> the study drug associated with the			
Total bilirubin (mg/dL)		toxicity.			
Total protein (g/dL)					
Albumin (g/dL)					

LDH (U/L)

^{*} If the collection date differs from the visit date for this visit, explain: ______.

Mg/Placebo Toxicity Check

Visit 10

Page: 6a of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	Mg/Placebo Toxicity Check	Visit 10 Page: 6a of 8			
Sickle Cell Centers	,				
Hydroxyurea &		CSCC ID:			
Magnesium Pidolate (CHAMPS)		Center code:			
		Hospital code:			
All questions relate to events since the previous visit.					
1) Since the last visit diarrhe	a has/is: Diarrhea was not evaluated at this vi	sit			
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 G	uidelines for grading criteria.			
→ For all Gr	ades complete AE form				
→ For Grade	3 complete SAE form if subject is hospitalized				
→ For Grade	• 4 complete SAE form				
Duration:	_dayshours				
2) Since the last visit abdom	inal pain has/is: Abdominal pain was not	evaluated at this visit			
Resolved Ongoin	g Worsened New Not present a previous visit	t this visit and was not present at the			
→ If ongoing, worsened, or new, is pain severe enough to interfere with daily Yes No activities?					
→ If resolved or on	going 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 Ongoin	ng Worsened New Not present a previous visit	at this visit and was not present at the			
→ 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?					
→ 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.

HU/Placebo Toxicity Check

Visit 10

Page: 6b of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.	

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Comprehensive Sickle Cell Centers	HU/Placebo Toxicity Check	Visit 10	Page: 6b of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID:	nter code:
		Hos	pital code:

All questions relate to events since the previous visit.

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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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		

Urinalysis

Visit 10

Page: 7 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 10 Page: 7 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:
*C0	Day Month Year	
☐ Labs not do →Specify:_		
Protein (Select one, as re	eported by your lab):	
Negative T	Trace 100 200 300 1+	2+ 3+
Microscopic RBC (#/mn	n³):	
Negative C	-5 5-10 10-25 25-50	50+
Microscopic WBC (#/mi	m ³):	
Negative C	-5 5-10 10-25 25-50	50+

† If the collection date differs from the visit date for this visit, explain: ______.

Pregnancy Test

Visit 10

Page: 8 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 10 Page: 8 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Prognancy Tost
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

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



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

If this visit is also serving as a Toxicity Visit:

- □ Chemistry Panel²
- Chemistry Lab CRF
- 2) Sodium, Potassium, Chloride, CO2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH



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
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

Interim Health History

Visit 11

Page: 1 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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		
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 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		
7	Treatment Location: Date of Encounter: Physician's Office / Clinic Day Month Year Emergency Department / Day Hospital / Urgent Care Day Month Year		
Re	Date Admitted: Date Discharged: Hospital Day Month Year Day Month Year Reason(s)¹: Pain crisis² ACS³ Fever Acute splenic sequestration Clinical stroke Cancer Priapism Hepatic sequestration		
·	2) Has the subject had any pain crisis(es) at home⁴ for which there was no hospitalization or emergency department/day hospital/urgent care visit? → 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	Select one: Month Year Number	OR units/cc's unknown
	Reason: Exacerbation of anemia due to an aplastic crisis Preparation for anesthesia	Exacerbation of anemia ACS and due to splenic sequestration Other, specify	Other complication of sickle cell disease (CNS event, priapism, AVN)
² A pa	rgency Department, clinic, or provider's office	pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours, and is not explained except by sickle cell disease. ary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, whe	

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Comments for page

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⁴ 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.



Comprehensive Sickle Cell Centers	Physical Exam	Visit 11 Page: 2 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

hysical Exa	am
Not	t Done → Specify:
1) Weigl	ht¹: (kg)
-	e spleen palpable? Yes² No If yes, what is the current spleen size? (at the greatest distance below the left costal margin)
-	he subject have any new skin lesions? Yes² No If yes, where are the lesions located:
	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.

 $^{^{\}rm 2}$ If yes, update or add to the AE page as appropriate.

Hematology Labs

Visit 11

Page: 3 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

Comprehensive Sickle Cell Centers	Н	lematology Labs		Vis	it 11	Pag	e: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)				CSC	Ce	enter code:	
*Co	llection Dat	re: / /	/		Hos	pital code:	
☐ Labs not done → Specify:		Day Month	Ye.	ar			
TEST		VALUE		ELE	CTRO	PHORES	SIS
Hemoglobin (g/dL)			Hb	A (%)]. [
Hematocrit (%)				Not Done - No re transfusion or Hb ≤ 10 at previous			or Hb A (%)
RBC (x10 ⁶ /mm ³)				Not Done - Suspe Hb A (%) > 10			
WBC (x10 ³ /mm ³)					HU/F	Placebo	
MCV (fl)				ANC < 10		ty Checl	k!
MCHC (g/dL)			F		count <	75 x10³/mı	m ³
Platelet count (x10 ³ /	mm³)					or > 13.5	g/dL
% Retic				Either		OR ARC sovided.	should be
OR ARC (x10 ³ /mm ³)			-	Use th		unit for this study visits.	
ANC (x10 ³ /mm ³)							
collection date differs from the	ne visit date	for this visit, explain:					_·

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 11

Page: 4 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 \geq 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

Hydroxyurea & Magnesium Pidolate (CHAMPS) Was a chemistry lab conducted for evaluation of toxicity? If yes, complete this page. If no, leave the remainder of the page blank. *Collection Date: Day Month Year TEST VALUE HU/Placebo Renal Toxicity Check Conter code:	Comprehens Sickle Cell Cer		Chemistry Lab	S	Visit 11 Page: 4 of 6
→ If yes, complete this page. → If no, leave the remainder of the page blank. *Collection Date: Day Month Yes No Yes No HU/Placebo HU/Placebo	Magnesiur	n			Center code:
TEST VALUE HU/Placebo	→ If yes, com	plete this	s page.	Yes	s No
		*Colle	, , , , , , , , , , , , , , , , , , , ,]/ Year	
	TEST		VALUE		1101110100

TEST	VA	LUE
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: ___

Mg/Placebo Toxicity Check

Visit 11

Page: 5a of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.

Comprehen Sickle Cell Ce		•	g/Placeb icity Che		Visit '	11	Pag	e: 5a	of 6
Hydroxyure Magnesiu Pidolate (CH/	ım				CSCC II		r code:		
						Hospital	code:		
<u>-</u>		since the previou	<u>s visit</u> .						
1) Since the last vis	sit diarrhea l	nas/is: Dia	arrhea was no	ot evaluated at the	his visit				
Resolved	Ongoing	Worsened	New	Not prese	nt at this visit a risit	ind was no	t prese	nt at th	ie
→ If new, or	going, or w	orsened:							
Grade:	1	2 3	4 → See C	CRF Completio	n Guidelines	for gradir	ng crite	eria.	
→	For all Grad	es complete AE for	m						
		complete SAE form	-	s hospitalized					
→	For Grade 4	complete SAE forn	1						
Duration	n:d	ayshou	rs						
2) Since the last vi	sit abdomina	al pain has/is:	Abdo	minal pain was	not evaluate	ed at this	visit		
Resolved	Ongoing	Worsened	New	Not pres previous	ent at this visit visit	and was r	not pres	ent at	the
→ If ongoing activities?	→ If ongoing, worsened, or new, is pain severe enough to interfere with daily Yes No activities?								
→ If reso	lved or ongo	ing modify AE Fori	m as approp	riate					
→ If new,	add AE to A	E Form							
3) Since last visit s	igns of dehy	/dration have/are?		Dehydration w	as not evalua	ated at thi	s visit		
Resolved	Ongoing	Worsened	New	Not pres	sent at this visit	t and was i	not pres	sent at	the
→ If resolved or ongoing modify AE Form as appropriate									
→ If new, add AE to AE Form									
4) Does/did subjec	t meet criter	ia for Mg/Placebo	toxicity*?	Y	es 🔲 I	No			
→ If yes, complete an AE Form.									
5) What action was	5) What action was taken with Mg/Placebo?								
→ If withheld o	r modified , ւ	ipdate the Mg/Place	ebo Study D	rug Dosing Lo	g				

^{*} 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.

HU/Placebo Toxicity Check

Visit 11

Page: 5b of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 11	je: 5b of 6
Hydroxyurea &		CSCC ID:	
Magnesium Pidolate (CHAMPS)		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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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

Pregnancy Test

Visit 11

Page: 6 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 11 Page: 6 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
, ,		Hospital code:

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:	



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



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
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

Interim Health History

Visit 12

Page: 1 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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-regord other pain crisis information should be obtained primarily from the medical record secondarily by subject's self-report. Any information determined by subject 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 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:		
	Has the subject had <u>acute e</u> department/day hospital/urg	s since the previous study visit. vents that led to a visit to physician's office/clinicent care facility, or a hospitalization? utton and record information for each event	c/ emergency Yes No		
٦	Freatment Location: Physician's Office / Clinic Emergency Department / Day Hospital / Urgent Car	Day Month Year			
Re	Date Admitted: Date Discharged: Hospital Day Month Year Day Month Year Reason(s)¹: Pain crisis² ACS³ Fever Acute splenic sequestration Clinical stroke Priapism Hepatic sequestration Other, specify				
	hospitalization or emergence → If yes, how many pain cris Blood Transfusion?	Yes No	Yes No ADD		
→ If yes, click the "ADD" button and record date and number of units or cc's for each transfusion. Select one:					
	Reason: Exacerbation of anemia due to an aplastic crisis 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)				
² A pa Eme	rgency Department, clinic, or provider's office	ain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours, and is not explained except by sickle cell disease. ary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, whe			

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Comments for page

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⁴ 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.



Comprehensive Sickle Cell Centers	Physical Exam	Visit 12 Page: 2 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

hysic	cal Exam
[Not Done → Specify:
1	I) Weight¹: (kg)
2	2) Is the spleen palpable? ☐ Yes² ☐ No → If yes, what is the current spleen size? cm (at the greatest distance below the left costal margin)
3	3) Did the subject have any new skin lesions?
4	I) 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.

Hematology Labs

Visit 12

Page: 3 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10. 	

Comprehensive Sickle Cell Centers				Visit 12	Pag	e: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)					Center code:	
*Col	Ilection Date: Day	/ Month	/ Year]	ospital code:	
Labs not done → Specify:						
TEST	v	ALUE		ELECTR	OPHORES	SIS
Hemoglobin (g/dL)]. [Hb A	(%)		
Hematocrit (%)					Not Done - Not ransfusion o	r Hb A (%)
RBC (x10 ⁶ /mm ³)					Not Done - S Hb A (%) > 1	
WBC (x10 ³ /mm ³)				HU	l/Placebo	
MCV (fl)			AN	Toxio C < 1000/mr	city Check	<u></u>
MCHC (g/dL)			Pla		< 75 x10 ³ /mr	n ³
Platelet count (x10 ³ /	mm³)				dL or > 13.5	g/dL
% Retic]. []	Į.		ic <u>OR</u> ARC sl provided.	hould be
OR ARC (x10 ³ /mm ³)					e unit for this I study visits.	subject
ANC (x10 ³ /mm ³)						

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

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Chemistry Labs

Visit 12

Page: 4 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.	

Comprehensive Sickle Cell Centers Hydroxyurea & Magnesium Pidolate (CHAMPS)	Chemistry L	Page: 4 of 6 CSCC ID: Center code: Hospital code:			
*Collection Date:					
TEST	VALUE				
Sodium (mmol/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			
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)		If toxicity occurs, <u>stop</u> the study drug associated with the			
Total bilirubin (mg/dL)		toxicity.			
Total protein (g/dL)					
Albumin (g/dL)					

LDH (U/L)

^{*} If the collection date differs from the visit date for this visit, explain: ______.

Mg/Placebo Toxicity Check

Visit 12

Page: 5a of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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:	
All mostions relate to some		Hospital code:	
All questions relate to ever	<u> </u>		
1) Since the last visit diarrhe	a has/is: Diarrhea was not evaluated at this vi	sit	
Resolved Ongoing	Worsened New Not present at previous visit	this visit and was not present at the	
→ If new, ongoing, or worsened:			
Grade: ☐ 1 ☐ 2 ☐ 3 ☐ 4 → See CRF Completion Guidelines for grading criteria.			
→ For all Gr	ades complete AE form		
	e 3 complete SAE form if subject is hospitalized		
→ For Grad e	e 4 complete SAE form		
Duration:	_dayshours		
2) Since the last visit abdom	inal pain has/is: Abdominal pain was not	evaluated at this visit	
Resolved Ongoir	ng Worsened New Not present a previous visit	t this visit and was not present at the	
→ If ongoing, worsene activities?	ed, or new, is pain severe enough to interfere with da	ily Yes No	
→ If resolved or or	ngoing modify AE Form as appropriate		
→ If new , add AE to	O AE Form		
3) Since last visit signs of dehydration have/are? Dehydration was not evaluated at this visit			
Resolved Ongoin	ng Worsened New Not present a previous visit	at this visit and was not present at the	
→ 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*?			
→ If yes, complete an Al	E Form.		
5) What action was taken with Mg/Placebo?			
→ If withheld or modified	d, 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.

HU/Placebo Toxicity Check

Visit 12

Page: 5b of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 12 Page: 5b of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
,		Hospital code:

All questions relate to events since the previous visit.

1 · · · · · · · · · · · · · · · · · · ·			
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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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			

Pregnancy Test

Visit 12

Page: 6 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 12 Page: 6 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Pregnancy Test	
Not Done (C	Check reason below)
Subjec	ct male
Subjec	t has not reached menstruating age
Postme	enopausal
Hyster	ectomy
Tubal l	igation
Other,	specify:
	n: Day Month Year Serum Urine Positive Negative

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



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

If this visit is also serving as a Toxicity Visit:

- □ Chemistry Panel²
- Chemistry Lab CRF
- 2) Sodium, Potassium, Chloride, CO₂, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH



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
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

Interim Health History

Visit 13

Page: 1 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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:		
A	All questions relate to events	since the previous study visit.			
1)		vents that led to a visit to physician's office/clinicent care facility, or a hospitalization?	c/ emergency Yes No		
	→If yes, click the "ADD" but	atton and record information for each event			
-	Freatment Location:	Date of Encounter:			
	Physician's Office / Clinic	Day Month Year			
	Emergency Department / Day Hospital / Urgent Car	e Day Month Year			
Re	Date Hospital Day ason(s)¹:	Admitted: Date Discharged: Date Discharged: Day Month Year Day Month Year Year Day Month Year Year Day Month Year Day Day Day Month Year Year Day Month Year Day Month Year Year Day Month Year Day Month Year Year Day Month Month	ar		
	Pain crisis ²	ACS ³ Fever Acc	ute splenic sequestration		
	Clinical stroke	Cancer Priapism He	patic sequestration		
L	Other, specify				
2)		n crisis(es) at home ⁴ for which there was no y department/day hospital/urgent care visit?	Yes No		
	→ If yes, how many pain cris	es were treated at home:			
3)	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	Select one: Units Cc's Cc's	OR units/cc's unknown		
	Reason: Exacerbation of anemia due to an aplastic crisis	Exacerbation of anemia ACS and due to splenic sequestration	Other complication of sickle cell disease (CNS event, priapism, AVN)		
	Preparation for anesthesia	Other, specify			
² A pa Eme	rgency Department, clinic, or provider's office	ain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours and is not explained except by sickle cell disease. ary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, whe			

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Comments for page

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⁴ 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.

Comprehensive Sickle Cell Centers	Interim Health History	Visit 13 Page: 2 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

All questions relat	e to events since	Visit 10.					
cer							
		en diagnosed wit		Serious Adverse	Yes Event forms	No No as appropriat	te.
Date diagnos	ed: Day	/ Month Y	/ear	Type:			
							AD
roimaging							
→ Complete of	one record for ea	ach type of test.					
Type of test ¹ : (check one)	MRI	MRA []ст [Cerebral angiography	Ot	her,specify	
	sult abnormal?	Yes²	No No	Equivocal ³			

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

Comprehensive Sickle Cell Centers	Physical Exam	Visit 13 Page: 3 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
,		Hospital code:

hysi	cal Exam
	Not Done → Specify:
	1) Weight ¹ : (kg)
	2) Is the spleen palpable? ☐ Yes² ☐ 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? ☐ Yes² ☐ 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.

Hematology Labs

Visit 13

Page: 4 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

Comprehensive Sickle Cell Centers	Hematology Lab	Visit 13 Page: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code: Hospital code:
☐ Labs not done	llection Date: Day Month	Year
TEST	VALUE	ELECTROPHORESIS
Hemoglobin (g/dL)		Hb A (%)
Hematocrit (%)		Not Done - No recent transfusion or Hb A (% ≤ 10 at previous visit
RBC (x10 ⁶ /mm ³)		Not Done - Suspect Hb A (%) > 10
WBC (x10 ³ /mm ³)		HU/Placebo
MCV (fl)		Toxicity Check! ANC < 1000/mm ³
MCHC (g/dL)		Platelet count < 75 x10³/mm³ Hb ≥ 20% ↓ from Visit 1
Platelet count (x10 ³ /	mm³)	Total Hb < 5 g/dL or > 13.5 g/dL
% Retic OR ARC (x10³/mm³)		Either % Retic <u>OR</u> ARC should be provided. Use the same unit for this subject at all study visits.
		1

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 13

Page: 5 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 \geq 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

Comprehens Sickle Cell Cer		C	Chemistry La	bs		Visit 13		ge: 5 of	f 7
Hydroxyurea Magnesiur Pidolate (CHAI	n					CSCC ID:	Center code Hospital code:		
Was a chemistry → If yes, com → If no, leave	plete this	page.	valuation of toxicity?		Yes	s 🗌	No		
	*Colle	ection Date:	Day Month	/	ear				
TEST		VAL	.UE				Placebo exicity Chec	k	
Creatinine (mg/dL)		\neg \Box	Not required						-

TEST	VA	LUE
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.

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^{*} If the collection date differs from the visit date for this visit, explain: ___

Mg/Placebo Toxicity Check

Visit 13

Page: 6a of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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:
All questions relate to ever	ute since the province visit	Hospital code:
<u> </u>		
1) Since the last visit diarrhe Resolved Ongoing		sit
→ If new, ongoing, or	worsened:	
Grade: 1	2 3 4 → See CRF Completion Gu	idelines 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:dayshours		
2) Since the last visit abdom	inal pain has/is:	evaluated at this visit
Resolved Ongoin	g Worsened New Not present a previous visit	t this visit and was not present at the
→ If ongoing, worsene activities?	d, or new, is pain severe enough to interfere with da	ily Yes No
→ If resolved or or → If new, add AE to	g oing modify AE Form as appropriate o AE Form	
3) Since last visit signs of do	ehydration have/are? Dehydration was no	ot evaluated at this visit
Resolved Ongoin	ng Worsened New Not present a previous visit	t this visit and was not present at the
→ If resolved or ongoing modify AE Form as appropriate → If new, add AE to AE Form		
4) Does/did subject meet cri → If yes, complete an AB	teria for Mg/Placebo toxicity*? Yes	☐ No
5) What action was taken wit	h Mg/Placebo? No change Withhe	ld Modified
→ If withheld or modified	d, 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.

HU/Placebo Toxicity Check

Visit 13

Page: 6b of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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?
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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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

Pregnancy Test

Visit 13

Page: 7 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 13 Page: 7 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

Not Done (Check reason below) Subject male Subject has not reached menstruating age Postmenopausal Hysterectomy Tubal ligation Other, specify: *Date of Collection: Day Type: Serum Urine	
Subject has not reached menstruating age Postmenopausal Hysterectomy Tubal ligation Other, specify:	
Postmenopausal Hysterectomy Tubal ligation Other, specify: *Date of Collection: Day Month Year	
Hysterectomy Tubal ligation Other, specify: *Date of Collection: Day Month Year	
Tubal ligation Other, specify: *Date of Collection: Day Month Year	
*Date of Collection: Day Month Year	
Day Month Year	
Day Month Year	
Type: Serum Urine	
Result: Positive Negative	

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



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 Visi	t 15 to CHAMPS_labs@rhoworld.com
	lectrophoresis is repeated as needed until the subject's Hb %A ≤ 10%. come in for another test prior to Visit 15 for another electrophoresis.

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

Page 1 of 1 January 29, 2007





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
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 Fourteen

(Month 10 +/- 8 days)

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

Interim Health History

Visit 14

Page: 1 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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:				
Expected Date of Next Visit:	·	Hospital code:				
Has the subject had <u>acute of</u> department/day hospital/urg	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 Yes No department/day hospital/urgent care facility, or a hospitalization?					
→If yes, click the "ADD" b	utton and record information for each event					
Treatment Location: Physician's Office / Clinic	Date of Encounter: Day Month Year					
	Emergency Department / Day Hospital / Urgent Care Day Day Month Year					
Date Admitted: Date Discharged: Date Discharged: Date Discharged:						
Reason(s) ¹ :]					
Pain crisis ²	ACS ³ Fever Ac	tute splenic sequestration				
Clinical stroke	Cancer Priapism He	epatic sequestration				
Other, specify						
	n crisis(es) at home ⁴ for which there was no y department/day hospital/urgent care visit?	Yes No ADD				
→ If yes, how many pain cris	ses 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	Select one: Month Year Number Cc's	OR units/cc's unknown				
Reason:						
Exacerbation of anemia due to an aplastic crisis	Exacerbation of anemia Exacerbation of anemia ACS Other complication of sickle cell					
Preparation for anesthesia	Other, specify					
hospital, Emergency Department, clinic, or provide	pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hourser's office; and is not explained except by sickle cell disease. hary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, whe					

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⁴ 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</u> <u>not</u> be considered a painful crisis at home.



Comprehensive Sickle Cell Centers	Physical Exam	Visit 14 Page: 2 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

1) Weight ¹ : (kg)			
2) Is the spleen palpable? ☐ Yes² → If yes, what is the current spleen size?	No cm	ance below the le	eft costal margin)
3) Did the subject have any new skin lesions? → If yes, where are the lesions located:	Yes ²	☐ No	

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.

Hematology Labs

Visit 14

Page: 3 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

Comprehensive Sickle Cell Centers	Hem	atology Lab	S	Visit 14	Page	e: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)					nter code:	
*Co	ollection Date:	Day Month	/		oital code:	
☐ Labs not done → Specify:	,		1001			
TEST		VALUE		ELECTROF	PHORES	IS
Hemoglobin (g/dL)			Hb A	A (%)]. 🗆	
Hematocrit (%)				tra	ot Done - No Insfusion or 10 at previo	· Hb A (%
RBC (x10 ⁶ /mm ³)					ot Done - So o A (%) > 10	
WBC (x10 ³ /mm ³)				HU/P	lacebo	
MCV (fl)			Δ1	Toxicit NC < 1000/mm ³	y Check	!
MCHC (g/dL)			PI	atelet count < 7 $ \ge 20\% \downarrow \text{ from } $		3
Platelet count (x10 ³	/mm³)			otal Hb < 5 g/dL		ı/dL
% Retic			-	Use the same u	vided.	
ARC (x10 ³ /mm ³) ANC (x10 ³ /mm ³)			L	at all St	auy violto.	

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 14

Page: 4 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.

Comprehensive Sickle Cell Centers	Chemistry L	Abs Visit 14 Page: 4 of 6	
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code: Hospital code:	
*C ☐ Labs not done → Specify:	ollection Date: Day	Month Year	
TEST	VALUE		
Sodium (mmol/L)		HU/Placebo Renal Toxicity Check SGPT > 2x upper limit of normal	
Potassium (mmol/L)			
Chloride (mmol/L)			
CO ₂ (mmol/L)		HU/Placebo	
BUN (mg/dL)		Renal Toxicity Check Creatining > 1.2 mg/dl, subjects < 18 years of ago	
Creatinine (mg/dL)		Creatinine ≥ 1.2 mg/dL subjects < 18 years of age Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age	
Calcium (mg/dL)			
SGPT/ALT (U/L)			
Alk phosphatase (U/L)		If toxicity occurs, <u>stop</u> the study drug associated with the toxicity.	
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: ______.

Mg/Placebo Toxicity Check

Visit 14

Page: 5a of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	Mg/Placebo Toxicity Check	Visit 14 Page: 5a of 6		
Sickle Cell Centers	Toxicity Officer	r ager oa or o		
Hardware of 0		CSCC ID:		
Hydroxyurea & Magnesium		Center code:		
Pidolate (CHAMPS)				
		Hospital code:		
All questions relate to even	ts since the previous visit.			
1) Since the last visit diarrhe	a has/is: Diarrhea was not evaluated at this vi	sit		
Resolved Ongoing	Worsened New Not present at to previous visit	his visit and was not present at the		
→ If new, ongoing, or	·			
Grade: 1	2 3 4 → See CRF Completion Gu	idelines for grading criteria.		
→ For all Gr	ades complete AE form			
→ For Grade	3 complete SAE form if subject is hospitalized			
→ For Grade	e 4 complete SAE form			
Duration:dayshours				
2) Since the last visit abdominal pain has/is: Abdominal pain was not evaluated at this visit				
Resolved Ongoir	g Worsened New Not present a previous visit	t this visit and was not present at the		
→ If ongoing, worsened, or new, is pain severe enough to interfere with daily Yes No activities?				
→ If resolved or or	ngoing modify AE Form as appropriate			
→ If new , add AE to	o AE Form			
3) Since last visit signs of do	ehydration have/are? Dehydration was no	ot evaluated at this visit		
Resolved Ongoin	ng Worsened New Not present a previous visit	t this visit and was not present at the		
→ 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?				
→ 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.

HU/Placebo Toxicity Check

Visit 14

Page: 5b of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 14	Page: 5b of 6	6
Hydroxyurea & Magnesium		CSCC ID:	ter code:	
Pidolate (CHAMPS)			tal 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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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		

Pregnancy Test

Visit 14

Page: 6 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 14 Page: 6 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

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

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



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 Hold off on labs until the next visit IF subject has been: 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

If this visit is also serving as a Toxicity Visit:

- Chemistry Panel²
- □ Chemistry Lab CRF
- 2) Sodium, Potassium, Chloride, CO₂, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH



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
is the subject taking any medication: List
Please record any other information from this visit for which there is no source document:
Signature Date



RhoLAB Specimen ID Tracker January 4, 2007

Subject ID Number _____ Visit Date _____ 10-mL lavender vacutainer Place here 10-mL lavender vacutainer Place here 5-mL green vacutainer Place here 5-mL lavender vacutainer

Place

here



Visit Fifteen

(Month 11 +/- 8 days)

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

Interim Health History

Visit 15

Page: 1 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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:
ļ	All questions relate to events	since the previous study visit.	
		vents that led to a visit to physician's office/clinicent care facility, or a hospitalization?	c/ emergency Yes No
	→If yes, click the "ADD" but	utton and record information for each event	
1	Freatment Location:	Date of Encounter:	
	Physician's Office / Clinic	Day Month Year	
	Emergency Department / Day Hospital / Urgent Car	e Day Month Year	
	Date	Admitted: Date Discharged:	
	Hospital Day	Month Year Day Month Ye	ar
Re	ason(s)¹:	_	
	Pain crisis² Clinical stroke		ute splenic sequestration
	Other, specify	Cancer Priapism He	patic sequestration
		n crisis(es) at home ⁴ for which there was no y department/day hospital/urgent care visit?	Yes No
3)	Blood Transfusion?	Yes No	
	→ If yes, click the "ADD" be	utton and record date and number of units or cc's for	r each transfusion.
	Date Transfused: Day	Select one: Units Cc's Cc's	OR units/cc's unknown
	Reason:	_	_
	Exacerbation of anemia due to an aplastic crisis	Exacerbation of anemia due to splenic sequestration	Other complication of sickle cell disease (CNS event, priapism, AVN)
	Preparation for anesthesia	Other, specify	
² A pa Eme	rgency Department, clinic, or provider's office	tain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours, and is not explained except by sickle cell disease. ary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, whe	

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Comments for page

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⁴ 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.



Comprehensive Sickle Cell Centers	Physical Exam	Visit 15 Page: 2 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

1) Weight ¹ : (kg)			
2) Is the spleen palpable? ☐ Yes² → If yes, what is the current spleen size?	No cm	ance below the le	eft costal margin)
3) Did the subject have any new skin lesions? → If yes, where are the lesions located:	Yes ²	☐ No	

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.

Hematology Labs

Visit 15

Page: 3 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

Comprehensive Sickle Cell Centers	Hematolo	gy Labs	Visit 15	Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)				Center code:
*Co	Ilection Date:	// _		ospital code:
☐ Labs not done → Specify:	Day	Month `	Year	
TEST	VAI	LUE	ELECTR	OPHORESIS
Hemoglobin (g/dL)		.	Hb A (%)	
Hematocrit (%)		.		Not Done - No recent transfusion or Hb A (% ≤ 10 at previous visit
RBC (x10 ⁶ /mm ³)]		Not Done - Suspect Hb A (%) > 10
WBC (x10 ³ /mm ³)]. [HU	/Placebo
MCV (fl)]. 🗌 📗	ANC < 1000/mr	city Check!
MCHC (g/dL)]. 🗌	Platelet count : Hb ≥ 20% ↓ fro	< 75 x10 ³ /mm ³
Platelet count (x10 ³ /	/mm³)			dL or > 13.5 g/dL
% Retic OR ARC (x10³/mm³)]. 🗆	Use the sam	ic <u>OR</u> ARC should be provided. e unit for this subject I study visits.
		1		

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 15

Page: 4 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 \geq 2x the upper limit of normal this is considered a toxicity, and appropriate dose reduction procedures must be followed.

Comprehens Sickle Cell Cer		Chemistry La	bs	Visit 15 Page: 4 of 6
Hydroxyurea Magnesiur Pidolate (CHAI	n			CSCC ID: Center code: Hospital code:
→ If yes, com	plete this	ducted for evaluation of toxicity? s page. ainder of the page blank.	Ye	s No
	*Colle	ection Date: Day Month	/ Year	
TEST		VALUE		HU/Placebo Renal Toxicity Check
o .: : / /!!>		Not so suite al		

TEST	VA	LUE
Creatinine (mg/dL)		Not required
SGPT/ALT (U/L)		Not required

HU/Placebo Renal Toxicity Check	
GGPT > 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.

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^{*} If the collection date differs from the visit date for this visit, explain: ___

Mg/Placebo Toxicity Check

Visit 15

Page: 5a of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 is persists for more than 72 hours OR if there are signs of dehydration from dial if the subject has abdominal pain severe enough to interfere with daily activities.		

Comprehensive	Mg/Placebo Toxicity Check	Visit 15 Page: 5a of 6
Sickle Cell Centers	TOXICITY CHECK	r age. 3a or 0
		CSCC ID:
Hydroxyurea & Magnesium		Center code:
Pidolate (CHAMPS)		Center code.
		Hospital code:
All questions relate to even	its <u>since the previous visit</u> .	
1) Since the last visit diarrhe	a has/is: Diarrhea was not evaluated at this	visit
Resolved Ongoing		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 Gr	ades complete AE form	
→ For Grade	e 3 complete SAE form if subject is hospitalized	
→ For Grade	e 4 complete SAE form	
Duration:	_dayshours	
2) Since the last visit abdom	inal pain has/is: Abdominal pain was n	ot evaluated at this visit
Resolved Ongoir	g Worsened New Not present previous vis	t at this visit and was not present at the sit
→ If ongoing, worsene activities?	ed, or new, is pain severe enough to interfere with	daily Yes No
→ If resolved or or	ngoing modify AE Form as appropriate	
→ If new , add AE to	AE Form	
3) Since last visit signs of de	ehydration have/are? Dehydration was	not evaluated at this visit
Resolved Ongoin	ng Worsened New Not presen previous vi	nt at this visit and was not present at the sit
→ If resolved or ongoi	ng modify AE Form as appropriate	
→ If new, add AE to AE	Form	
4) Does/did subject meet cri	teria for Mg/Placebo toxicity*?	No
→ If yes, complete an AE	Form.	
5) What action was taken wit	h Mg/Placebo? No change With	held Modified
→ If withheld or modified	d, 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.

HU/Placebo Toxicity Check

Visit 15

Page: 5b of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 15 Page: 5	5b of 6
Hydroxyurea &		CSCC ID:	
Magnesium Pidolate (CHAMPS)		Center code:	
		Hospital code:	

All questions relate to events since the previous visit.

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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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

Pregnancy Test

Visit 15

Page: 6 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers	Pregnancy Test	Visit 15 Page: 6 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

	Not Done (Check reason below)
	Subject male
	Subject has not reached menstruating age
	Postmenopausal
	Hysterectomy
	Tubal ligation
	Other, specify:
*Da	te of Collection: Day Month Year
	Type: Serum Urine
	Result: Positive Negative

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



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 	
•	ne/she has a guess into which arm he/she was randomized, and 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, CO2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH



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
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

Interim Health History

Visit 16

Page: 1 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 click the 'ADD' button for each location</u>. 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 	
Pain Crises	CHAMPS page on the CSCC website. 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 Yes No department/day hospital/urgent care facility, or a hospitalization? →If yes, click the "ADD" button and record information for each event					
Treatment Location:	Date of Encounter:				
Physician's Office / Clinic	Treatment Location: Date of Encounter: Physician's Office / Clinic Day Month Year				
Emergency Department / Day Hospital / Urgent Ca					
Date Admitted: Date Discharged: Hospital /					
Reason(s) ¹ :	Month Year Day Month Ye				
Pain crisis ²	ACS ³ Fever Ac	ute splenic sequestration			
Clinical stroke	Clinical stroke Cancer Priapism Hepatic sequestration				
Other, specify					
2) Has the subject had any pain crisis(es) at home⁴ for which there was no hospitalization or emergency department/day hospital/urgent care visit? → 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 Cc's OR units/cc's unknown					
Reason:					
Exacerbation of anemia due to an aplastic crisis					
Preparation for anesthesia	Other, specify				
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.					

Comments for page

⁴ 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.

Compreher Sickle Cell C		Health History	Visit 16		e: 2 of 7	7
Hydroxyur	a &		CSCC ID:			
Magnesi Pidolate (CH				Center code:		
			ŀ	Hospital code:		

er? Yes No	
t and Serious Adverse Event forms as appropriate.	
Type: Location:	
	,
ing procedures? Yes No	
est/type.	
est/type.	
est/type. Cerebral Other,specify angiography	
	Location:

- 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.

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Comprehensive Sickle Cell Centers	Physical Exam	Visit 16 Page: 3 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

hysical Exam	
Not Done → Specify:	
1) Weight ¹ : (kg)	
2) Is the spleen palpable? Yes² → If yes, what is the current spleen size?	No cm (at the greatest distance below the left costal margin)
3) Did the subject have any new skin lesions? → If yes, where are the lesions located:	☐ Yes² ☐ No
4) Has subject taken any new medications since → If yes, complete the Concomitant Medication	

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.

 $^{^{\}rm 2}$ If yes, update or add to the AE page as appropriate.

Hematology Labs

Visit 16

Page: 4 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10. 	

Comprehensive Sickle Cell Centers	Hematology Lab	S Visit 16 Page: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
*Coll	ection Date: / /	Hospital code:
☐ Labs not done → Specify:	Day Month	Year
TEST	VALUE	ELECTROPHORESIS
Hemoglobin (g/dL)		Hb A (%)
Hematocrit (%)		Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit
RBC (x10 ⁶ /mm ³)		Not Done - Suspect Hb A (%) > 10
WBC (x10 ³ /mm ³)		HU/Placebo
MCV (fl)		Toxicity Check! ANC < 1000/mm ³
MCHC (g/dL)		Platelet count < 75 x10³/mm³ Hb ≥ 20% ↓ from Visit 1
Platelet count (x10 ³ /n	nm³)	Total Hb < 5 g/dL or > 13.5 g/dL
% Retic		Either % Retic <u>OR</u> ARC should be provided. Use the same unit for this subject
ARC (x10 ³ /mm ³)		at all study visits.
ANC (x10 ³ /mm ³)		

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Visit 16

Page: 5 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	Instructions	
Collection Date	ion 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 reas 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.	

Comprehensive Sickle Cell Centers	Chemistry Labs	Visit 16 Page: 5 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code: Hospital code:
Labs not done → Specify:	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)	

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: _______.

Mg/Placebo Toxicity Check

Visit 16

Page: 6a of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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:
All questions relate to even	ts <u>since the previous visit</u> .	Hospital code:
1) Since the last visit diarrhea has/is: Diarrhea was not evaluated at this visit		
Resolved Ongoing		this visit and was not present at the
→ If new, ongoing, or	worsened:	
Grade: ☐ 1 ☐ 2 ☐ 3 ☐ 4 → See CRF Completion Guidelines for grading criteria.		
 → For Grade → For Grade Duration: 2) Since the last visit abdom ☐ Resolved ☐ Ongoin → If ongoing, worsene activities? 	inal pain has/is: Abdominal pain was not g Worsened New Not present a previous visit d, or new, is pain severe enough to interfere with da	at this visit and was not present at the
3) Since last visit signs of dehydration have/are? Dehydration was not evaluated at this visit		
Resolved Ongoir	ng Worsened New Not present a previous visit	at this visit and was not present at the
→ 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*?		
→ If yes, complete an AE Form.		
5) What action was taken wit	h Mg/Placebo? No change Withhe	eld 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.

HU/Placebo Toxicity Check

Visit 16

Page: 6b of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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% \downarrow from Visit 1 3. Platelet count < 75 x10 ³ /mm ³ 4. Total Hb < 5 or > 13.5 g/dL		
3) Hematologic toxicity?		
If any toxicity is new , resolved or ongoing modify AE Form as appropriate		

Urinalysis

Visit 16

Page: 7 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 Page: 7 of 7
Hydroxyurea & Magnesium		CSCC ID: Center code:
Pidolate (CHAMPS)		Hospital code:
* C d ☐ Labs not do →Specify:_		
Protein (Select one, as re	eported by your lab): Trace	2+ 3+
Microscopic RBC (#/mn	n ³): 0-5	50+
Microscopic WBC (#/mi		<u> </u>

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



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 	
•	he/she has a guess into which arm he/she was randomized, and like to remain on study drug. Record on the Study Completion CRF.	
	emember that AEs should be followed until resolved.	

- 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

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.



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
is the subject taking any medication: List
Please record any other information from this visit for which there is no source document:
Signature Date



RhoLAB Specimen ID Tracker January 4, 2007

Subject ID Number _____ Visit Date _____ 10-mL lavender vacutainer Place here 10-mL lavender vacutainer Place here 5-mL green vacutainer Place here 5-mL lavender vacutainer

Place

here

Early Termination

- Interim Health History
- Physical Exam
- Hematology Labs
- Chemistry Labs
- Toxicity Check
- Urinalysis

Interim Health History

Early Termination

Page: 1 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 CHAMDS page on the CSCC website.
Pain Crises	CHAMPS page on the CSCC website. 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 Page: 1 of 7
	Hydroxyurea & Magnesium Pidolate (CHAMPS)	Date of Visit: Day Month Year	CSCC ID: Center code: Hospital code:
P	all questions relate to events	since the previous study visit.	
		vents that led to a visit to physician's office/clinicent care facility, or a hospitalization?	c/ emergency Yes No
	→If yes, click the "ADD" bu	utton and record information for each event	
7	reatment Location:	Date of Encounter:	
	Physician's Office / Clinic	Day Month Year	
	Emergency Department / Day Hospital / Urgent Car	re Day / Month / Year	
	Date Hospital Day	Admitted: Date Discharged: Month	ar
Re	ason(s)¹:	·	
	Pain crisis ²	ACS ³ Fever Ac	ute splenic sequestration
	Clinical stroke	Cancer Priapism He	patic sequestration
	Other, specify		
		n crisis(es) at home ⁴ for which there was no y department/day hospital/urgent care visit? es were treated at home:	Yes No ADD
3)	Blood Transfusion?	Yes No	
	→ If yes, click the "ADD" be	utton and record date and number of units or cc's for	r each transfusion.
	Date Transfused: Day	Select one: Units Cc's Cc's	OR units/cc's unknown
	Reason:		
	Exacerbation of anemia due to an aplastic crisis	Exacerbation of anemia ACS due to splenic sequestration	Other complication of sickle cell disease (CNS event, priapism, AVN)
	Preparation for anesthesia	Other, specify	
² A pa Eme	rgency Department, clinic, or provider's office	nain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours, and is not explained except by sickle cell disease.	

Comments for page

⁴ 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.

Comprehensive Sickle Cell Centers	Interim Health History	Early Termination Page: 2 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

er	o events since	ino proviodo visit.						
	sit, has this su	bject been diagno	osed with ca	ncer?	Ye	s	No	
If yes, record deta	ails below and o	complete Adverse E	Event and Se	erious Adve	rse Event forn	ns as appr	opriate.	
Date diagnosed:	Day	Month Year		ype: _ ocation: _				
								Al
oimaging								
	record for eac	h type of test.						
Date of test:	/	th type of test.						
Date of test:	precord for each		ст 🔲	Cerebral angiograp	ohy C	Other,spec	ify	
Date of test: Type of test¹: (check one) Was this result	Day Mont	/ Year MRA	CT		ohy —	Other,spec	ify	

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

Comprehensive Sickle Cell Centers	Physical Exam	Early Termination Page: 3 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

hysic	cal Exam
[Not Done → Specify:
1	I) Weight¹: (kg)
2	2) Is the spleen palpable? ☐ Yes² ☐ 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? ☐ Yes² ☐ 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.

 $^{^{\}rm 2}$ If yes, update or add to the AE page as appropriate.

Hematology Labs

Early Termination

Page: 4 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

Comprehensive Sickle Cell Centers	Hematology Labs	Early Termination Page: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
*Collect	ion Date: /	Hospital code:
☐ Labs not done → Specify:	Day Month	Year
TEST	VALUE	ELECTROPHORESIS
Hemoglobin (g/dL)		Hb A (%)
Hematocrit (%)		Not Done - No recent transfusion or Hb A (%) ≤ 10 at previous visit
RBC (x10 ⁶ /mm ³)		Not Done - Suspect Hb A (%) > 10
WBC (x10 ³ /mm ³)		HU/Placebo
MCV (fl)		Toxicity Check! ANC < 1000/mm ³
MCHC (g/dL)		Platelet count < 75 x10³/mm³ Hb ≥ 20% ↓ from Visit 1
Platelet count (x10³/mm³)	Total Hb < 5 g/dL or > 13.5 g/dL
% Retic		Either % Retic <u>OR</u> ARC should be provided.
OR ARC (x10 ³ /mm ³)		Use the same unit for this subject at all study visits.
ANC (x10 ³ /mm ³)		

If toxicity occurs, $\underline{\text{stop}}$ the study drug associated with the toxicity.

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Chemistry Labs

Early Termination

Page: 5 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.	

Comprehensive Sickle Cell Centers	Chemistry Labs	Early Termination Page: 5 of 7
Hydroxyurea & Magnesium		CSCC ID:
Pidolate (CHAMPS)		Center code: Hospital code:
*(Collection Date: Day Month / Year	
Labs not done → Specify:	e	

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: _______.

Mg/Placebo Toxicity Check

Early Termination

Page: 6a of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 Page: 6a of 7
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:dayshours
_
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 Yes No activities?
→ 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*?
→ If yes, complete an AE Form.
5) What action was taken with Mg/Placebo?
→ 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.

HU/Placebo Toxicity Check

Early Termination

Page: 6b of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	Early Termination 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?		
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 \geq 20% \downarrow 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		

Urinalysis

Early Termination

Page: 7 of 7

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 the lab was not done.		

Comprehensive Sickle Cell Centers	Urinalysis	Early Termination Page: 7 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
* C c ☐ Labs not do →Specify:_		Hospital code:
Protein (Select one, as re	eported by your lab): frace	2+ 3+
Microscopic RBC (#/mn	n ³): -5	<u></u> 50+
Microscopic WBC (#/mi		<u>50+</u>

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

CSCC Comprehensive Sickle Cell Centers Clinical Trials Consortium

No opinion

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 Subject randomized?	ets who are at least 14 years of age:	In your opinion	, into whi	ch arm	were you
	– HU & Mg.	f marked:				
	0	Would you want to continue using	HU? Yes	No	Don't	Know
	0	Would you want to continue using I	Mg? Yes	No	Don't	Know
	- HU Placebo	& Mg. If marked:				
	0	Would you want to continue using I	Mg? Yes	No	Don't	Know
	- HU & Mg P	acebo. If marked:				
	0	Would you want to continue using	HU? Yes	No	Don't	Know
	- HU Placebo	& Mg Placebo				
	- No opinion					
_	•	t/guardian of all Subjects who are le s the subject randomized?	ss than 18 years	s of age:	In you	r opinion, into
	– HU & Mg.	f marked:				
	0	Would you want the subject to conf	tinue using HU?	Yes	No	Don't Know
	0	Would you want the subject to conf	tinue using Mg?	Yes	No	Don't Know
	- HU Placebo	& Mg. If marked:				
	0	Would you want the subject to conf	tinue using Mg?	Yes	No	Don't Know
	- HU & Mg P	acebo. If marked:				
	0	Would you want the subject to con-	tinue using HU?	Yes	No	Don't Know
	- HU Placebo	a & Mg Placebo				

- □ 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.





CHAMPS Source Document Worksheet For Study Completion CRF

Dat	Date: / CSCC ID:				
NO	TE: If subje	ct lost to follow-up, include copy of certified letter in Subject Binder			
Dat	te of Last Vi	it:			
		complete the study? □ Yes □ No			
	If no, r	cord the date of last contact and select the primary reason for early withdrawal from below			
	Date o	Last Contact:			
Po:	asons for Ea	rly Withdrawal:			
		tigator's opinion the subject's health, safety and/or continued participation in the study			
		s nonadherent. Specify:			
_	•	to follow-up			
	-	ubject's legal representative requested to withdraw Specify:			
_	-	tion (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 adve	se event or significant concurrent illness			
	Other	Specify:			
<u>Inv</u>		n your opinion, into which arm was the subject randomized?			
	· ·				



CHAMPS Source Document Worksheet For Study Completion CRF

<u>Stı</u>	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				
Su	bjects who are at least 14 years of age: In your o	pinion, ir	nto whic	h 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				
	rent/Guardian of all Subjects who are less than 1	8 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				
Ple	ease record any other information from this visit	for whic	h there	is no source document:	
Sic	gnature	Date			



Study Completion

Page: 1 of 3

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	ry 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.	

Comprehensive Sickle Cell Centers	Study Completion	Page: 1 of 3	
Hydroxyurea &		CSCC ID:	
Magnesium Pidolate (CHAMPS)		Center code:	
		Hospital code:	
Date of last visit:	//		
Did the subject complete t	he study? Yes No		
→ If no, record the date of	last contact and select the primary reason for early v	withdrawal from below.	
Date of last contact:	Day Month Year		
Reasons for early witho	Irawal:		
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	Subject or subject's legal representative requested to withdraw.		
Specify:	Specify:		
Discontinuation (c	heck all that apply)		
Decline in Hb le	evel to < 5 g/dL		
Increase in Hb	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		

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Other, Specify:

Other adverse event or significant concurrent illness,

Specify:

Study Completion

Page: 2 of 3

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	Instructions	
Investigator Opinion This question should always be asked.		
Study Coordinator Opinion This question should always be asked.		

Comprehensive Sickle Cell Centers	Study Completion	Page: 2 of 3
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code: Hospital code:
Hydroxyurea 8 Hydroxyurea F Hydroxyurea 8	ich arm was this subject randomized? Magnesium Magnesium Placebo Placebo & Magnesium Placebo	
Hydroxyurea 8 Hydroxyurea F Hydroxyurea 8	ich arm was this subject randomized? Magnesium Magnesium Placebo Placebo & Magnesium Placebo Placebo & Magnesium Placebo	

Study Completion

Page: 3 of 3

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 the 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 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.	

Comprehensive Sickle Cell Centers	Study Completion	Page: 3 of 3		
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:		
Tidolato (OTIZIIII O)		Hospital code:		
	if the Subject is at least 14 years of age; skip to 'ote that you will also ask this question of the Pare 18.			
In your opinion, into which	n arm were you randomized?			
Hydroxyurea & Ma	ignesium. If marked:			
	t to continue using Hydroxyurea? Yes No	☐ Don't know		
→ Would you wan	t to continue using Magnesium? Yes No	☐ Don't know		
Hydroxyurea Place	ebo & Magnesium. If marked:	Bont know		
→ Would you wan	t to continue using Magnesium? $\ \ \ \ \ \ \ \ \ \ \ \ \ $	Don't know		
• •	gnesium Placebo. If marked:			
	t to continue using Hydroxyurea? Yes No	☐ Don't know		
No opinion	Soo a Magnesiam Flacebo			
	t a 14 years ald			
☐ Not asked, subject	•			
☐ Not asked, other re	Specify:			
Parent/Guardian: Ask this	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 & Ma	gnesium. If marked:			
• •	→ Would you want the subject to continue using Hydroxyurea? ☐ Yes ☐ No ☐ Don't know			
→ Would you wan	→ Would you want the subject to continue using Magnesium?			
Hydroxyurea Place	ebo & Magnesium. If marked:			
	t the subject to continue using Magnesium? Ye	s No Don't know		
→ Would you wan	t the subject to continue using Hydroxyurea? $\ \ \ \ \ \ \ \ \ \ \ $ Ye	s No Don't know		
☐ Hydroxyurea Place	Hydroxyurea Placebo & Magnesium Placebo			
☐ No opinion	No opinion			
Not asked, subject ≥ 18 years old				
Not asked, parent/guardian was not present at this visit				
Not asked, other re	Not asked, other reason:			
Specify:				
Investigator's Statement:				
	entries within this CRF and, to the best of my knowle ecord of the subject's participation in the study.	dge, the data represent a		
PI signature:	Signature Date: Da	y Month Year		



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 <i>or</i> 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

If the toxicity IS NOT resolved

 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.

If the toxicity IS resolved

- □ 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*

Hematology Labs

Toxicity Visit

Page: 1 of 4

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 (%) ≤ 10 at previous visit" if no recent transfusion or if electrophoresis was not performed because Hb A (%) ≤ 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 (%) ≤ 10.

Comprehensive Sickle Cell Centers	F	lematology Labs		Тох	kicity Visit Page: 1 of	4
Hydroxyurea & Magnesium Pidolate (CHAMPS)				csc	Center code: Hospital code:	
Was a hematology lab c →If yes, complete this →If no, leave the remains	page.			Yes	No No	
*Co	llection Da	te: Day Month]/ [Year		
TEST		VALUE		ELE	ECTROPHORESIS	
Hemoglobin (g/dL)			-	Hb A (%)		
Hematocrit (%)					Not Done - No recer transfusion or Hb A (≤ 10 at previous visit	(%)
RBC (x10 ⁶ /mm ³)					Not Done - Suspect Hb A (%) > 10	
WBC (x10 ³ /mm ³)					HU/Placebo	
MCV (fl)				ANC < 1	Toxicity Check! 000/mm³	
MCHC (g/dL)				Platelet	count < 75 x10³/mm³ % ↓ from Visit 1	
Platelet count (x10 ³ /	/mm³)				o < 5 g/dL or > 13.5 g/dL	
% Retic				Either	% Retic <u>OR</u> ARC should be provided.	•
OR ARC (x10 ³ /mm ³)				Use th	he same unit for this subject at all study visits.	
ANC (x10 ³ /mm ³)						
e collection date differs from t	he visit date	for this visit, explain:				

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

Chemistry Labs

Toxicity Visit

Page: 2 of 4

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.

	_					Toxicity	y Visit		
Comprehens Sickle Cell Cer		C	Chemistry La	bs				ge: 2 d	of 4
Hydroxyurea Magnesiur Pidolate (CHAI	n					CSCC ID:	Center code:		
Was a chemistry → If yes, com → If no, leave	plete this	page.	valuation of toxicity?		Yes	s	No		
	*Colle	ection Date:	Day Month	/	'ear				
TEST		VAI	_UE				Placebo exicity Checl	k	
Creatinine (mg/dL)		\neg _ \Box	Not required				-		

TEST	VAI	LUE
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.

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^{*} If the collection date differs from the visit date for this visit, explain: _

Mg/Placebo Toxicity Check

Toxicity Visit

Page: 3 of 4

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 Page: 3 of 4
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:dayshours
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 Yes No activities?
→ 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*?
→ If yes, complete an AE Form.
5) What action was taken with Mg/Placebo?
→ 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.

HU/Placebo Toxicity Check

Toxicity Visit

Page: 4 of 4

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 Page: 4 of 4
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?	
1) Hepatic toxicity?	
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	
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age Creatinine ≥ 1.4 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/mm³ 2. Hb ≥ 20% ↓ from Visit 1 3. Platelet count < 75 x10³/mm³ 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	



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 <i>generic</i> 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 &		CSCC ID: Center code:
Magnesium Pidolate (CHAMPS)		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	Stop Date	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



CHAMPS Source Document Worksheet AE for Painful Crisis

Date: /	<i>I</i>	CSCC ID:					
Since the previous study visit, has this subject experienced a painful crisis? Yes 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:	-				
□ Chest	Type of Pain □ Typical □ Atypical	Outcome: Resolved without sequel Resolved with sequelae Ongoing Death					
Relationship to study drug Unrelated Probably not related/re Possibly related Possibly related Definitely related Hospitalization	- 	Action Taken: No action Study treatment interrupted Study treatment discontinu Study treatment dose adju Concomitant medication gi ER/Day Hospital Hospitalization	ued sted				
As a result of this AE, was	s the subject tra	nsfused? □ Yes □ N	No				
Did the pain event evolve	into another ad	verse event? □ Yes □ N	No				
Please record any other in	nformation from	this visit for which there is no s	source document:				
Signature							

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 or 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
111		CSCC ID:
Hydroxyurea & Magnesium Pidolate (CHAMPS)		Center code:
, , ,		Hospital code:
omplete this form for each	pain event.	
Was this a Serious Adverse E	Event?	ubmit an SAE report to SDMC?
Date of onset:	/ Date of resolution:	Day Month Year
Location of Pain (Check a	II that apply)	
Chest	Abdomen Leg(s)	
Back	Arm(s) Head & Neck	
Type of Pain		
Typical Atypic	cal	
What was the outcome?	(Check one)	
Resolved without sec	quelae Resolved with sequelae 0	Ongoing
Present at death, no	t contributing to death Death due to this A	AE .
What was the level of severit	y? (Check one)	
Mild - Home	Moderate - ER Severe - H	lospital
What was the relationship to	study drug(s)? (Check one)	
	robably not Possibly related Probelated / remote	ably related Definitely related
What action was taken?	(Check all that apply)	
No Action	Concomitant Medication Giver	n
Study Treatment Inte	errupted ER/Day Hospital	
Study Treatment Dis	continued Hospitalization	
Study Treatment Do	se Adjusted	

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→ If yes, complete the transfusion section of the Interim Health History form.

→ If yes, complete an Adverse Event form and specify Adverse Event.

Yes

Yes

No

No

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As a result of this AE, was the subject transfused?

Did the pain event evolve into another adverse event?

Adverse Event, specify



CHAMPS Source Document Worksheet for AEs (non-pain)

Date: / /	CSCC ID:							
□ * Yes □ No *If Yes, list below.	Did the subject List all condition	•	•	`	U .	,		
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) Modera 3) Severe 4) Life-thra 5) Fatal		 Unrela Probab Possib Probab 	Study Drug ³ ted oly not/remote ly related oly related ely related	Ac 1) 2) 3) 4) 5) 6)	Study drug Study drug Concomita Hospitaliza	ospital	
Signature		 Da	te					

AE Not for Painful Crisis

Ongoing

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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 &		CSCC ID: Center code:
Magnesium Pidolate (CHAMPS)		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 Day Month Year	N No Y Yes				
2	N No Y Yes	Day Month Year Day Month Year Day Month Year	N No Y Yes				
3	N No Y Yes	Day Month Year Day Month Year Day Month Year	N No Y Yes				
4	N No Y Yes	Day Month Year Day Month Year Day Month Year	N No Y Yes				
7 11DEC2007	1 OUTCOME 1 = Resolved witl 2 = Resolved witl 3 = Medically sta 4 = Present at de 5 = Death 6 = Ongoing	h sequelae 2 = Mode ble 3 = Sever	rate	3 RELATIONSHII 1 = Unrelated 2 = Probably not/remote 3 = Possibly rela 4 = Probably rela 5 = Definitely rela	1 = N 2 = St 3 = St ted 4 = C ated 5 = H ated 6 = El	ION TAKEN one tudy treatment inter tudy treatment disco oncomitant medicat ospitalization R/Day hospital ther, specify	ontinued

☐ Initial Report☐ Follow-up Report	CS	CC Comprehensive Si	ckle Cell C	enters	CSC	DID:	
			Clinical Trials C	onsortium		Center co	ode:
"Effectiveness of H	RSE EXPERIENC ydroxyurea and Mag Disease: A Phase II	nesium Pidolate Alone and in Trial"	Combination t Date (DD/MN		If ti	Hospital co	ode: te of Initial Report
Site Name:		, 	_/	/			•
Subject's Date of Bi	rth:						
Subject's Weight: _	lbs./ kgs.	Subject ⁴	s Gender: 🗆 N	√lale □ Fer	male		
Please indicate SAI the following Death			STUDY PR Complete the	ODUCT De the Table be			
Immediately Life-Persistent/Signifination	•	Study Product Name	Dose, R Schedule of Product(s) Onse	of Study at SAE	S	dy Product tart Date MMM/YYYY)	Study Product Stop Date (DD/MMM/YYYY)
 Hospitalization/Prolonged Hospitalization Congenital Anomaly/Birth Defect Serious as assessed by the Investigator 		Hydroxyurea/ Placebo					☐ Ongoing
		Magnesium Pidolate/ Placebo					□ Ongoing
		* Document the complete dosi					
Event (Keyword or Cause of Death)	Date of Onset (DD/MMM/YYYY)	Severity (Select only one)		nship to St Product ect only one	•		ATED, what is the t related to:
		☐ Grade 1 (Mild) ☐ Grade 2 (Moderate) ☐ Grade 3 (Severe) ☐ Grade 4 (Life-Threatening ☐ Grade 5 (Death)	☐ Possi	ably not/Ren bly ably	note	study proces specify other condspecify other drug? specify	lition/illness?
	Charles Dans	duct Ctatus			Ch.	! C!-!!	D
As a result of		duct Status ove. Check one item only in each col	umn.		Subj	ect Status/0	Julcome
Hydroxyure	a/Placebo	Magnesium Pidolate/Pl	acebo	☐ Ongoin	g		
☐ Study Product Admin☐ Study Product Admin	·	☐ Study Product Administration☐ Study Product Administration☐	-	□ Resolved without sequelae Date///			Date// (DD/MMM/YYYY)
□ Study Product Admin □ Dose Adjust	istration Deferred	☐ Study Product Administration ☐ Dose Adjust		□ Resolve	ed with	n sequelae 🛚 🛭	Date/// (DD/MMM/YYYY)
Specily		Specify		States	sequel	ae:	
☐ Participation terminat☐ Other, <i>specify:</i>	, ,	☐ Participation terminated by Inv☐ Other, <i>specify:</i>	· ·	□ Death	□ N □ C □ F	opsy: Not Done Done (Provide F Planned Status Unknown	•

"Effectiveness of Hy in Hemoglobin SC I	RSE EXPERIENCE In Advanced in Tries of the American American Control of the Am	sium Pidolate Alone a al"	nd in Combination Report Date (DD/MMM,	Center Hospital	code: date of Initial Report
	ory of event, associated edical history below, <u>or</u>		alternative etiologies	being considered, medica ecessary.)	al management
List relevant abnormal			ND indicate pertinent re	sults on the copy. (Use ad	ditional pages if
necessary.) □ Summa Test	Collection Date (DD/MMM/YYYY)	Abnormal Result	Normal Range	Lab Value Previous to this SAE	Collection Date
			c results AND indicate p	ertinent results on the copy	. (Use additional
Test	Date Perfor (DD/MMM/Y		Res	sults/Comments	
	,				

☐ Initial Report☐ Follow-up Report #	CSCC	Comprehensive Sickl	e Cell Centers	CSCC ID:	
		Ü	linical Trials Consortium	Center code:	
	EXPERIENCE REPO				
Effectiveness of Hydrom n Hemoglobin SC Disea		Pidolate Alone and in Cor	nbination	Hospital code:	
•		Report Da	te (DD/MMM/YYYY)	If this is a F/U, date of	Initial Report
Site Name:		/_		/	
CONCOMITANT MED No relevant concomitant					
nedications, please make		taking up to 1 month prior to m and report all concomitant		bject was taking more than	n 6
Medication (generic name)	Start Date	Stop Date	Dose	Indication	Suspect
l.	//_ DD/MMM/YYYY	//	□ Unknown		□ Yes □ No
	// DD/MMM/YYYY	//	□ Unknown		□ Yes □ No
	// DD/MMM/YYYY	// DD/MMM/YYYY	□ Unknown		□ Yes □ No
	// DD/MMM/YYYY	// DD/MMM/YYYY	□ Unknown		□ Yes
	// DD/MMM/YYYY	// DD/MMM/YYYY	□ Unknown		□ Yes □ No
	//	//			□ Yes
			□ Unknown		
ompleted by (signature):		Completed by (prin	nt):	Date:	JI
vestigator (signature): _		Investigator (print)):	Date:	
Date Submitted ☐ IRB ☐ CSCC - DSME		(DD/MMM/Y) //	YYY) '	□ Not Applicable□ Not Applicable□ Not Applicable	

SERIOUS ADVERSE EXPERIENCE REPORT "Effectiveness of Hydroxyurea and Magnesium Pidola in Hemoglobin SC Disease: A Phase II Trial" Site Name:	Report Date (DD/MMM/YYYY)	CSCC ID: Center code Hospital code If this is a F/U, date	e: Initial Report
Additional Ir Include clinical history of event, associated signs and s and relevant past medical history below, or attach sum			inagement
Completed by (signature):	Completed by (print):	Date:	
Investigator (signature):	Investigator (print):	Date:	_//

(DD/MMM/YYYY)

Date Submitted/Faxed To:

□IRB

☐ CSCC - DSMB

☐ Other, *specify:*___

□ Not Applicable

□ Not Applicable

□ Not Applicable



Protocol Deviation Form

Ongoing

Page: 1a of 1

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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	
	Complete a separate form	for each deviation from the protocol.	Hospital	code:
C	Date of protocol deviation or ate when deviation was iscovered: Type of Deviation:	Day Month Year Was the subject F	?andomized?	No Yes
Г	1. Randomization or Mas	king Error Specify:		
L	1. Kandonnzation of Mas	king Error, opecity.		
Γ	2. Dosing Error, Specify:			
_	Did this lead to an over	dose? No Yes		
	3. Missed Visit, Record th	ne Visit Number:		
	Why was the visit mis	sed?		
	Caregiver wa			
	Scheduling of			
		rienced AE requiring hospitalization		
		erienced AE requiring visit to Clinic or Physician's office	ce	
	Subject expe	rienced AE requiring Emergency Dept/Day Hospital/	Urgent Care visit	
	Subject expe	erienced AE not requiring medical attention		
	Other, specif		i-t- \	
г	_	ie to AE, be sure to complete AE & SAE forms as app	propriate.)	
L	4. Mistimed Visit, Record			
	Did the visit occur too	early or too late? Too early Too	late	
_	How far outside the vi	sit window was the visit? days		
	-	r Laboratory Measure, Record the Visit Number:		
	Was the entire asses	sment mistimed?		
	No: Which p	eart of the assessment was mistimed?		
		assessment was mistimed? o-down, write in the title from CRF)		
	6. Missed Procedure or L			
	Was the entire asses	sment missed? art of the assessment was missed?		
		assessment was missed?		
		o-down, write in the title from CRF)		

Protocol Deviation Form

Ongoing

Page: 1b of 1

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

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.

Comprehensive Sickle Cell Centers	Protocol Deviatio (continued	_	Ongo	oing	Page 1b of 1
Hydroxyurea & Magnesium Pidolate (CHAMPS)			CSCCI	Cent	er code:
7. Inclusion Criteria Not	Met		<u> </u>		
Inclusion Number		·			. (drop-down, 1-6)
8. Exclusion Criteria No Exclusion Number	t Met				(drop-down, 1-9)
9. Informed Consent, E	xplain:				
10. Other, Specify: _					
Reason for Deviation:					
Steps Taken to Resolve a	nd Prevent Recurrence of Devi	ation:			
Did this deviation result in	n an adverse experience?	☐ No	Yes (If	yes, com	plete AE form.)
→ If yes, was the AE	serious? No Yes	(If yes, comple	ete SAE form.)	
Will the subject continue	with the study?	☐ No	Yes (If	no, comp	plete discontinuation forn
Is report to IRB required f	or this deviation?	☐ No	Yes		
→ If yes, Date reported:	Day Month Yea	ar			
If further action is require	d, describe it:				
Additional Comments:					

CSCC comp	rehensive Sickle Ce	II Centers			CSC	CC ID:		
	Clinical Ti	rials Consortium	Donor i			Center code	e:	
PREGNANCY NO "Effectiveness of Hydro: in Hemoglobin SC Disea Report Date (DD/MMM/Y	xyurea and Magnesium se: A Phase II Trial"	Pidolate Alone		nation		Hospital code	e:	
Subject's Date of Birth:	Sub	oject's Weight:	lbs	s./ kgs.	Subject's	s Gender: □ Male	e □ Female	
STUDY DRUG INFOR	MATION							
Study Product Name	Dose at Conception	Batch #	Time (of Exposur Trimester	e Delivery	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	
Hydroxyurea/ Placebo capsules (PO)	mg mg/kg/da					(DD/WWWW 1111)	(CD/MINIM 1111)	
Magnesium Pidolate/ Placebo (PO BID)	mEq mg/kg/da	у		□ 1 □ 2 □ 3				
CONCOMITANT MED List relevant medications ta Medication	ken before and during pre Start Date	Stop [r exposed, enter Date	medication Dose		to conception only	 Suspect	
(generic name)	DD/MMM/YYYY	DD/MMM	/				-	
				□ Unkno	wn		☐ Yes ☐ No	
2.				□ Unkno	wn		□ Yes □ No	
3.				□ Unkno	wn		□ Yes □ No	
4.			_/	□ Unkno	wn		□ Yes □ No	
5.		/	_/	□ Unkno			□ Yes □ No	
PREGNANCY INFORM	MATION							
LMP Date:	/							
Date of Last Negative Pr	Date of Last Negative Pregnancy Test:/							
Estimated Date of Delive	ry:	_!!	-					
Was estimated date corrected based on ultrasound? (Based on LMP)								

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.

Yes □ No □ N/A □

If "Yes" provide corrected date of delivery: ____/___

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PATERNAL INFORMATION

CSCC	Com	nprehensive Sickle Cell C	enters onsortium	CSO	CC ID: Center code:	
"Effectiveness of	of Hyd SC Dis D/MMN	, -			Hospital code:	
Contraception (may c	hoose 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	* item	ns above, please provide de	etails incl	uding dates & outcome as applic	able	
Was there a fam	ily hist	ory of birth defects? Yes E] No □	N/A □ If yes, describe the def	fects below:	

Was there a family history of birth defects? Yes \square No \square N/A \square 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.

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Signature:

Print Name:

CSCC comprehensive Sickle Cell Centers Clinical Trials Consortium						CSCC ID:	
PREGNANCY "Effectiveness of H in Hemoglobin SC I Report Date (DD/M	NOTIF ydroxyu Disease:		Center code: Hospital code:				
PREGNANCY STAT	ΓUS (Ch	eck 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					
Please submit an	n SAE fori	m.					
A threatened abortake place.	ortion is a	condition of pregnancy, occ	urring be	efore the 20th week of gestation	on, that s	suggests potential miscarriage may	
3. A missed abortion is when the embryo or fetus has died, but a miscarriage has not yet occurred.							
1. Therapeutic abortion: Therapeutic abortion is defined as the termination of pregnancy before fetal viability in order to preserve maternal health. (eMedicine.com)							

Date of Signature:

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.

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CSCC	01-14-0-11	A 4		C	,SCC ID:		
CSCC Comprehensive	Sickle Cell (Centers			Contor of	-do:	$\overline{\Box}$
PREGNANCY FOLLOW-U					Center co	oae:	Ш
"Effectiveness of Hydroxyurea and in Hemoglobin SC Disease: A Phas	Magnesium Pi	n	Hospital co	ode:			
PREGNANCY STATUS (Check all	that apply)						
Pregnancy Ongoing Prem	nature Delivery		Spontaneous abortion	on¹ □	Ectopic Pregnan	ісу	
Vaginal Delivery □ Stillb	oirth		Threatened abortion	n ²	Unknown		
C-section There	apeutic abortion	n ³ □	Missed abortion ⁴		Other (Provide of	details below)	
Forceps Elect	tive termination						
 Please submit an SAE form. A threatened abortion is a condition of pr A missed abortion is when the embryo or Therapeutic abortion is defined as the te RELEVANT LABORATORY TES	r fetus has died, bu rmination of pregna	ut a miscarria ancy before	age has not yet occurred. fetal viability in order to pres	serve maternal h	nealth. (eMedicine.con	n)	P)
Tests	Including units	Results Including units & normal values if applicable		Pending	Pre/Post Outcome?	Date DD/MMM/YY	ΥY
1					Pre □ Post □		
2					Pre □ Post □	_	
3					Post □ Pre □ Post □		
					POSI L		
Further details:							
							_
PREGNANCY OUTCOME Infant/Fetal Outcome:							
Unknown							
Lost to follow-up							
Number of infants/fetuses			t of more than 1 infant/ferm for each infant/fetus.)	etus, complete	Infant Information	section on a	
Normal baby							
Normal fetus							
Birth defect (structural/chromosomal)							
Other disorder (non-structural, premature birth)							
Death)ate:					

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.

Cause of death:

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		C	CSCC ID:	
renensive Sickle Ce	II Centers ials Consortium		Contar anda:	
xyurea and Magnesium ase: A Phase II Trial"	Pidolate Alone and in Co	mbination	Hospital code:	
			rior to concontion only	
Start Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Dose	Indication	Suspect
		□ Unknown		□ Yes □ No
		□ Unknown		□ Yes □ No
		□ Unknown		□ Yes □ No
		□ Unknown		□ Yes □ No
		□ Unknown		□ Yes □ No
Weight:lbskgs	Length: inch cm	Head Circumf	erence: inch cm	
livery/Abortion	(weeks)			
			_	
			No □	
	· ·			
	LOW-UP FORM xyurea and Magnesium se: A Phase II Trial" YYYY)/ ICATIONS	xyurea and Magnesium Pidolate Alone and in Cose: A Phase II Trial" YYYY)/	xyurea and Magnesium Pidolate Alone and in Combination se: A Phase II Trial* YYYY)	Center code: LOW-UP FORM kyurea and Magnesium Pidolate Alone and in Combination se: A Phase II Trial* Hospital code: YYY) ICATIONS

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.

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Print Name:

CSCC Comprehensive Sickle Cell Centers	CSCC ID:	
PREGNANCY FOLLOW-UP FORM	Center code:	
"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"	Hospital code:	
Report Date (DD/MMM/YYYY)/		

F	Report Date (DD/MMM/YYYY)//	/						
RE	LEVANT LABORATORY TESTS/PROCE	DURES FOR BABY/FETUS	5					
1	Tests	Results ing units & normal values if applica	Pen din able g □	Date DD/MMM/YYYY				
2								
3				·				
4								
	RTH DEFECT INFORMATION (Continue on re any birth defects noted? Yes \(\square\) No \(\square\)	(If yes, complete information be						
	Description of Birth Defect(s)	Attributable to ARV treatment? Y=Yes N=No U=Unknown	Other contributing factors: MA=Maternal Age U=Unknown O=O					
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.)								
AC	DDITIONAL INFORMATION (Continue on Sup	oplementary Form if necessary)						
Sig	Signature: Date of Signature:							

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.

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"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination

CSCC ID:	
Center code:	
Hospital code:	

PREGNANCY FOLLOW-UP FORM

in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY)// SUPPLEMENTARY INFORMATION FORM FOR PREGNANCY FOLLOW-UP FORM	
	RWITOR PREGNANCT TOLLOW-OF TORW
ADDITIONAL INFORMATION (Optional):	
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.

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