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.

Visit One

(Week 1)

- Inclusion Criteria V6.1
- Exclusion Criteria V6.1
- Screening
- Physical Exam
- Medical History
- Health History
- Hematology Labs
- Chemistry Labs
- Pregnancy Test
- Screen Failure Log for Visit 1

Inclusion Criteria V6.1

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 V6.1	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
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 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 (28 days)]?	Yes	No No
Note: Subjects enrolled under Protocol Version 6.0 are eligible if in steady state within the past 30 days.		

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 V6.1

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

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	
3. In the investigator's opinion, has the subject exhibited poor adherence with previous treatment regimens?	Yes No	
4. Has the subject had hepatic dysfunction (SGPT > 2x upper limit of normal) within the past month?	Yes No	
5. Has the subject had renal dysfunction (creatinine ≥ 1.0 mg/dL, < 18.0 years of age; ≥ 1.2 mg/dL, ≥ 18.0 years of age) within the past month?	Yes No	
6. Is the subject pregnant?	Yes No	
 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	
Has the subject had treatment with an investigational drug in last 3 months?	Yes No	
9. Does the subject have any other chronic illness or disorder other than SCD that could adversely affect the subject's performance in the study (e.g., tuberculosis)?	Yes No	

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

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 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) Result: Negative Month Year	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

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 Mor	th 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 (%) Other, s	pecify 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?	e left costal margin)
3) Does the subject have any skin lesions? ☐ Yes ☐ No → If yes, where are the lesions located:	
4) Is the subject taking any medication?	

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.

	onditions 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) Stroi (CNS) Othe		
			(Muscular, (Renal/Gen (Ocular) Re	lypersplenism Skeletal, Skin) Leg Ulcers intourinary) 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.

		story	isit 1	Page: 6	of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)		С	SCC ID:	Center code:	
			H	ospital code:	
rmation to be determined by patien	t interview and review of me	dical records.			
cer is the subject <u>ever had</u> or ever be	een diagnosed with cancer	? \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	□ No		
→ If yes, list the type(s) of cancer				d indicate whe	ether
present in the last year. Type of C	Cancer	Year of First	:	Present in La	ast Vear?
1,960 01 0		Diagnosis		Yes	□ No
				Yes	□ No
				Yes	□ No
roimaging					
→ If yes click the ADD button and	d, record details for each tes	normal findings? t/type.	Yes	s	∐ Not Don
Date of test: Day Month Type of test*: MRI MR	/			specify	
Date of test: Day Month Type of test*: MRI MR Briefly describe the findings: Date of test: Day Month	Year A CT Cereb	t/type.	Other,	specify	
Date of test: Day Month Type of test*: MRI MR Briefly describe the findings: Date of test: Day Month Type of test*: MRI MR	Year A CT Cereb	t/type.	Other,		
Date of test: Day Month Type of test*: MRI MR Briefly describe the findings: Date of test: Day Month Type of test*: MRI MR MRI MR Briefly describe the findings: ———————————————————————————————————	Year A CT Cereb	t/type.	Other,	specify	
Date of test: Day Month Type of test*: MRI MR Briefly describe the findings: Date of test: Day Month Type of test*: MRI MR Briefly describe the findings: Day Month Day Date of test*: Day Month	Year A CT Cereb Year A CT Cereb	t/type.	Other,	specify	
Date of test: Day Month Type of test*: MRI MR Briefly describe the findings: Date of test: Day Month MR Briefly describe the findings: Date of test*: MRI MR Briefly describe the findings: Date of test*: MRI MR MRI MR Day Month MR MRI MR MRI MR MRI MR MRI MR MR	Year A CT Cereb Year A CT Cereb	oral angiography	Other,	specify	
Date of test: Day Month Type of test*: MRI MR Briefly describe the findings: Date of test: Day Month Type of test*: MRI MR Month Type of test*: Day Month Date of test: Day Month Date of test: Day Month	Year A CT Cereb Year A CT Cereb Year A CT Cereb	oral angiography oral angiography oral angiography oral angiography	Other,	specify	

Visit 1

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Health History

Visit 1

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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 event	s in the past 12 months.		
3) Blood Transfusion?	Yes No		
→ If yes, click the "ADD" butt	on and record date and number of u	nits or cc's for e	each transfusion.
Date Transfused: Day	Month Year Number	Select one: units cc's	OR units/cc's unknown
Reason:			
Exacerbation of anemia due to an aplastic crisis	Exacerbation of anemia due to splenic sequestration	ACS _	Other complication of sickle cell disease (CNS event, priapism, AVN)
Preparation for anesthesia	Other, specify		
			ADD

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

Comments for page

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 Labs		Visit 1 Page: 8 of 11
Hydroxyurea & Magnesium Pidolate (CHAMPS)				CSCC ID: Center code:
				Hospital code:
*0	collection Date:	Day Month Y	ear/	

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

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	Chemistry Labs	Visit 1 Page: 9 of 11
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

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:

_	
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 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?			
→ 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, <i>Specify:</i>			
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			

Re-screening - Visit 1 (if applicable)

- Inclusion Criteria V6.1
- Exclusion Criteria V6.1
- 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 V6.1

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 V6.1	Re-screening – Visit 1
Sickle Cell Centers		Page: 1 of 8
Hydroxyurea &		CSCC ID:
Magnesium Pidolate (CHAMPS)	Date of Visit: / / / /	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 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
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 (28 days)]?	Yes	☐ No
Note: Subjects enrolled under Protocol Version 6.0 are eligible if in steady state within the past 30 days.		

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 V6.1

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		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? 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	
3. In the investigator's opinion, has the subject exhibited poor adherence with previous treatment regimens?	Yes	☐ No	
4. Has the subject had hepatic dysfunction (SGPT > 2x upper limit of normal) within the past month?	Yes	☐ No	
 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	

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)	Red Cell Density: % Hyperdense cells	% % hyperdense cells will be provide	ed via an e-mail from RhoLAB.
	If the subject has ≥ 3 percent	RBCs with density > 41 g/dL, he/she <u>is eligible</u> to continue	in this study.
2)	Hemoglobin Level:		
,	_	evel between 8 – 12.5 g/dL?	☐ No
	If the subject <u>has</u> a Hb level b	netween 8 – 12.5 g/dL, he/she <u>is eligible</u> to continue in this	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)	
٠,	4) HIV Status: (tested within the last 12 months) Date tested:		
	If the subject has a negative	HIV test, he/she <u>is eligible</u> to continue in this study.	
5)	Hepatic Dysfunction:		
	Within the past month, has the	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)	6) Renal Dysfunction:		
	Within the past month has su 1.2 mg/dL (if age 18.0 years	bject had creatinine \geq 1.0 mg/dL (if under age 18.0 year above)?	ears) or ≥ Yes No
	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:

			поѕрна соце.	
hysical Exam				
Not Done →	Specify		_	
1) Weight ¹ :	_ (kg)			
2) Is the spleen palp → If yes, what is the	he current spleen size?	No cm (at the greatest distance below the	left costal margin)	
	have any skin lesions? e the lesions located:	Yes No		
→ If yes , record in	ing any medication? formation on the Concomi to check "Pre-existing" on	Yes No tant Medications CRF. 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

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?)	

HEMA

Comprehensive Sickle Cell Centers	Hen	natology Labs	Re-screening – Visit 1 Page: 5 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)			CSCC ID: Center code:
			Hospital code:
*0	Collection Date:	Day Month Year	

TEST	VALUE	
Hemoglobin (g/dL)		
Hematocrit (%)		
RBC (x10 ⁶ /mm ³)		
WBC (x10 ³ /mm ³)		
MCV (fl)		
MCHC (g/dL)		
Platelet count (x10 ³ /mm ³)		
% Retic		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 Sickle Cell Centers	Chemistry Labs	Re-screening – Visit 1	
		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	3	Page: 7 of 8		
Hydroxyurea &		CSCC ID:		
Magnesium Pidolate (CHAMPS)		Center code:		
		Hospital code:		

gnancy Tes	t en
Not Dor	ne (Check reason below)
S S	ubject male
☐ St	ubject has not reached menstruating age
Po	ostmenopausal
☐ H ₃	ysterectomy
Tı	ubal ligation
Of	ther, specify:
_	
*Date of Colle	ction: Day Month Year
Type:	Serum Urine
Result:	Positive Negative

* 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 / Month / Year			
Primary Reason the subject will not be enrolled: (Check only one.)			
In the investigator's opinion, the subject's health, safety and/or well-being would be threatened by participation in the study.			
Subject lost to follow-up.			
Subject or subject's legal representative requested to withdraw. Specify:			
Subject did not meet inclusion/exclusion criteria.			
Is subject no longer in steady state after previously meeting inclusion/exclusion criteria? Yes No			
→ If Yes, check all that apply and complete the Adverse Event forms.			
Subject experienced one or more vaso-occlusive crises			
Subject experienced one or more non-vaso-occlusive sickle events			
Subject experienced one or more non-sickle related events			
Other Reason, Specify:			
Did subject complete the Re-screening Visit? Yes No			
→ If no, please provide the Date of Informed Consent at the Re-screening Visit.			
Date of Informed Consent: Day / Month / Year			
→ If yes, be sure to complete the Re-screening CRFs. Also update as appropriate, the 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, <i>Specify:</i>			
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			

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

- Inclusion Criteria V6.1
- Exclusion Criteria V6.1
- 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 V6.1

2nd Re-screening - Visit 1

Page: 1 of 8

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

ltem	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 V6.1	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 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 (28 days)]?	Yes	No No
Note: Subjects enrolled under Protocol Version 6.0 are eligible if in steady state within the past 30 days.		

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 V6.1

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	

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

	Comprehensive	Screening (Re-screen)	2nd 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)	Red Cell Density: % Hyperdense cells	% % hyperdense cells will be provide	ed via an e-mail from RhoLAB.	
	If the subject has > 3 percent	RBCs with density > 41 g/dL, he/she <u>is eligible</u> 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)	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: /		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	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 has not had SGPT > 2x upper limit of normal within the past month, he/she is eligible to continue in this study.			
6)	6) Renal Dysfunction:			
ŕ	-	bject had creatinine \geq 1.0 mg/dL (if under age 18.0 yr above)?	ears) or ≥ Yes No	
ĺ	Screening creatinine level (n	ng/dL) Local lab upper limit of n	ormal (mg/dL)	
ĺ	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	Hen	natology Labs		2nd Re-screening – Visit 1 Page: 5 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)			C	CSCC ID: Center code:
				Hospital code:
*C	Collection Date:	Day Month Y	/ear	

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

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 Boto.		

*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 &		CSCC ID:
Magnesium Pidolate (CHAMPS)		Center code: Hospital code:

nancy Te	
Not Do	ne (Check reason below)
	ubject male
□ s	ubject has not reached menstruating age
□ P	ostmenopausal
Пн	ysterectomy
П	ubal ligation
Пс	ther, specify:
Date of Colle	ection: Day Month Year
Type:	Serum Urine
Result:	Positive Negative

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

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	

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</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 2 Page: 1 of 7		
	Hydroxyurea & Magnesium Pidolate (CHAMPS)	Date of Visit: Day Month Year	CSCC ID: Center code: Hospital code:		
	All questions relate to events since the previous study visit. 1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency Yes No department/day hospital/urgent care facility, or a hospitalization?				
	→If yes, click the "ADD" be	utton and record information for each event			
٦	Freatment Location:	Date of Encounter:			
	Physician's Office / Clinic	Day Month Year			
	Emergency Department / Day Hospital / Urgent Car				
	Date	Admitted: Date Discharged:			
	Hospital Day	Month Year Day Month Ye	ar.		
Re	ason(s)¹:	World Teal Day World Te			
	Pain crisis²	ACS ³ Fever Ac	ute splenic sequestration		
	Clinical stroke	Cancer Priapism He	patic sequestration		
	Other, specify		pano 00 4400 nanon		
2)	Has the subject had any <u>pai</u> hospitalization or emergend	n crisis(es) at home ⁴ for which there was no ey 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.		
	<u> </u>	Select one:			
	Date Transfused: Day	Month Year Number units	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, specify	Other complication of sickle cell disease (CNS event, priapism, AVN)		
¹ Com	plete AE and/or SAE forms for each reason.		ADD		
² A pa Eme	in crisis is defined here as the occurrence of p rgency Department, clinic, or provider's office	oain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours; and is not explained except by sickle cell disease. Carry infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, who			
4 ^ ~ -	inful prints at home must be a new pullful	a standy estate situation. A pain print of home in defined as the comments	ois in the extremities, healt abdamen		

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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 visit.	
ancer	
Since Visit 1, has this subject been diagnosed with cancer?	
→ If yes, record details below and complete Adverse Event and Serious Adverse Event forms as appropriate.	
Date diagnosed: Day Month Year Location:	
	ADD
euroimaging	
Since Visit 1, has this subject undergone any neuroimaging procedures? → If yes, click the ADD button and record details for each type of test. → Complete one record for each type of test.	
Date of test: Day Month Year	
Type of test ¹ : MRI MRA CT Cerebral Other,specify angiography	
Was this result abnormal? Yes² No Equivocal³	
If yes, describe brief findings:	
	ADD

- 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:

hysid	nysical 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?		
4	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.

 $^{^{2}\,\}mathrm{lf}$ 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 reason the lab was not done.
Hemoglobin	The Hb level must be between 8.0 – 12.5 g/dL to be eligible for the study.

HEM2

Comprehensive Sickle Cell Centers	Не	matology Labs		Visit 2	Page: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)				CSCC ID:	Center code:
*c	ollection Date:]	Hospital code:
		Day Month	Year	l	
Labs not don → Specify:					
TES	ST	VALUE			
Hemoglobin (g/	dL)				
Hematocrit (%)					
RBC (x10 ⁶ /mm ³	8)				
WBC (x10 ³ /mm	³)				
MCV (fl)					
MCHC (g/dL)					
Platelet count (x	10 ³ /mm ³)				
% Retic					Retic <u>OR</u> ARC should be provided.
ARC (x10 ³ /mm ³)		—	Use the	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 Pidolate (CHAMPS)		CSCC ID: Center code:
*Co	ollection Date:///	Hospital code:
☐ Labs not do →Specify:_	Day Month Year ne	·
Protein (Select one, as re		
Negative T	race 100 200 300 1+	2+ 3+
Microscopic RBC (#/mn	n³):	
Negative 0	-5 5-10 10-25 25-50	50+
Microscopic WBC (#/mi	m³):	
Negative 0	-5 5-10 10-25 25-50	50+

* 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:

regnancy Test	
Not Done (Check reason belo	nw)
Subject male	
Subject has not reached	menstruating age
Postmenopausal	
Hysterectomy	
Tubal ligation	
Other, specify:	
*Date of Collection: Day	Month Year
Type: Serum L	Jrine
Result: Positive N	Negative

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

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
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.

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:				
	Has the subject had <u>acute e</u> department/day hospital/urg	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				
		utton and record information for each event					
	Freatment Location: Physician's Office / Clinic	Date of Encounter: Day Month Year					
	Emergency Department / Day Hospital / Urgent Car	Pe Day / Month / Year					
	Date Hospital Day	Admitted: Date Discharged:	lar.				
Re	ason(s)¹:						
	Pain crisis ²	ACS ³ Fever Ac	ute splenic sequestration				
	Clinical stroke	Cancer Priapism He	patic 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? → If yes, click the "ADD" be	Yes	r each transfusion.				
	Date Transfused: Day Month Year Number Cc's Select one:						
	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)				
<u> </u>	Preparation for anesthesia	Other, specify					
² A pa hosp	oital, Emergency Department, clinic, or provide	nain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours r'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, 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</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 Sickle Cell Centers	Н	ematology Labs		Visit	3	P:	age	: 2	of 5
Hydroxyurea & Magnesium Pidolate (CHAMPS)				CSCCI	Cer	nter cod			
*Cc	ellection Date	e: Day Month	/	ar	Hosp	ital code	e: 		
☐ Labs not done → Specify:									
TEST		VALUE		ELEC	TROF	PHOR	ESI	IS	
Hemoglobin (g/dL)			Hb	A (%)]. []		
Hematocrit (%)					— tra	ot Done Insfusio 10 at pr	n or	Hb A	A (%)
RBC (x10 ⁶ /mm ³)						ot Done A (%)			t
WBC (x10 ³ /mm ³)					HU/P	laceb	00		
MCV (fl)					Toxicity Check!				
MCHC (g/dL)		□.□	P	Platelet co	IC < 1000/mm ³ atelet count < 75 x10 ³ /mm ³ ≥ 20% ↓ from Visit 1				
Platelet count (x10 ³	/mm³)			otal Hb <			3.5 g	/dL	
% Retic		<u> </u>		Either %		DR ARO	C sh	ould I	be
OR ARC (x10 ³ /mm ³)			-	Use the		unit for t udy vis		subje	ct
ANC (x10 ³ /mm ³)									

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	Pa	age: (3 of 5	
Hydroxyurea & Magnesium Pidolate (CHAMPS)						CSCC ID:	Center cod			
Was a chemistry → If yes, com → If no, leave	plete this	s page.	raluation of toxicity?		Yes		No			
	*Colle	ection Date:	Day Month	/ Year	r					
TEST		VAL	.UE				Placebo xicity Che	ck		
Creatining (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

^{*} 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 Page: 4b of 5

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? 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? 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 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:

regnancy Test	
Not Done (Check reason belo	nw)
Subject male	
Subject has not reached	menstruating age
Postmenopausal	
Hysterectomy	
Tubal ligation	
Other, specify:	
*Date of Collection: Day	Month Year
Type: Serum L	Jrine
Result: Positive N	Negative

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

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:
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" be	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:	
	Hospital Day Month Year Day Month Year		
Re	eason(s)¹:		
	Pain crisis ²	ACS ³ Fever Acc	ute splenic sequestration
	Clinical stroke	Cancer Priapism He	patic sequestration
	Other, specify		
2) Has the subject had any pain crisis(es) at home ⁴ for which there was no hospitalization or emergency department/day hospital/urgent care visit?			
	→ 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: Month Year 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	
² A pa hosp	oital, Emergency Department, clinic, or provide	nain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours in soffice; 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</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:

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.

 $^{^{\}rm 2}$ 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	Не	matology Labs		Visit 4	Page	: 3 of 6
Hydroxyurea & Magnesium idolate (CHAMPS)				CSCC ID:	Center code:	
*Co	llection Date:]/ 🔲	Н	ospital code:	
☐ Labs not done → Specify:		Day Month	Yea			
TEST		VALUE		ELECTRO	OPHORESI	s
Hemoglobin (g/dL)			Hb /	A (%)		
Hematocrit (%)				Not Done - No rece transfusion or Hb A ≤ 10 at previous vis		
RBC (x10 ⁶ /mm ³)				Not Done - Suspect Hb A (%) > 10		ıspect)
WBC (x10 ³ /mm ³)				HU	/Placebo	
MCV (fl)	[Toxicity Check! ANC < 1000/mm³ Platelet count < 75 x10³/mm³		
MCHC (g/dL)		<u>.</u> .	P			
Platelet count (x10 ³ /	/mm³)			Hb ≥ 20% \downarrow from Visit 1 Total Hb < 5 g/dL or > 13.5 g/dL		
% Retic		<u>.</u> .	[ic <u>OR</u> ARC sho provided.	ould be
OR ARC (x10 ³ /mm ³)					e unit for this s I study visits.	subject
			1			

If toxicity occurs, <u>stop</u> 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 ≥ 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 Page: 4 of 6	
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 No	
	*Colle	ection Date:	Day Month	Year]	
TEST		VAL	.UE		HU/Placebo Renal Toxicity Check	
o / /!!\			☐ 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 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		Р	age	e: 5a	of	6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID:	Cent	er co	de:			
		ŀ	Hospit	al cod	de:			

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 days have
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

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: 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 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:

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

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

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	5
	Hydroxyurea & Magnesium Pidolate (CHAMPS)	Date of Visit: Day Month Year	CSCC ID: Cente	er code:	
	Expected Date of Next Visit:	Day Month Year → Email date	e to CHAMPS_la	bs @rhoworld.co	om
	•	since the previous study visit.	_	_	
1)		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			
-	Freatment Location:	Date of Encounter:			
	Physician's Office / Clinic	Day Month Year			
	Emergency Department / Day Hospital / Urgent Ca				
Re	Date Hospital Day Pason(s)¹:	Admitted: Date Discharged: January Januar	ear		
	Pain crisis ²	ACS ³ Fever Ac	ute splenic seque	estration	
	Clinical stroke	Cancer Priapism He	patic sequestration	on	
	Other, specify				
2)		n crisis(es) at home ⁴ for which there was no	Yes	No	ADD
		y department/day hospital/urgent care visit? ses were treated at home:	_	_	
3)	Blood Transfusion?	Yes No			
,		utton and record date and number of units or cc's fo	r each transfusio	n.	
		Select one:			
	Date Transfused: Day	Month Year Number units	OR units	cc's unknown	
	Reason: Exacerbation of anemia due to an aplastic crisis Preparation for anesthesia	Exacerbation of anemia ACS and ACS and ACS and ACS are due to splenic sequestration and ACS are of the ACS and ACS are due to splenic sequestration and ACS are are also are due to splenic sequestration.		ation of sickle c event, priapism	
² A pa		pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours	s; requires a visit to a hos	pital,	ADD
		; and is not explained except by sickle cell disease. ary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, whe	eezing, cough, or chest pa	in.	
⁴ A pa	inful crisis at home must be a new event, not	a steady state situation. A pain crisis at home is defined as the occurrence of p	pain in the extremities, bac	ck,	

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:

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 5

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	5 Page:	3 of 6		
Hydroxyurea & Magnesium Pidolate (CHAMPS)				CSCC II	Center code:			
*Co	llection Date	te: /]/ 🔲		Hospital code:			
☐ Labs not done → Specify:		Day Month	Yea	ar	_			
TEST		VALUE		ELEC	TROPHORESIS			
Hemoglobin (g/dL)			Hb	A (%)				
Hematocrit (%)					transfusion or H	Not Done - No recent ransfusion 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)				T(
MCHC (g/dL)			F	ANC < $1000/\text{mm}^3$ Platelet count < $75 \times 10^3/\text{mm}^3$ Hb $\geq 20\% \downarrow \text{ from Visit 1}$				
Platelet count (x10 ³ /	/mm³)				5 g/dL or > 13.5 g/d	L		
% Retic OR ARC (x10 ³ /mm ³)			→	Use the s	Retic <u>OR</u> ARC shown provided. same unit for this substant all study visits.			
,			1					

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

CHE3

Comprehens Sickle Cell Cer		(Chemistry	Labs		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.		city?	Yes	s 📗	No	
	*Collec	ction Date:	Day N	/ Innth Y	ear ear			
TEST		VAI	LUE				/Placebo oxicity Check	
Creatinine (mg/dL)		7.	Not require	ed				

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

HU/Placebo Renal Toxicity Check	
GPT > 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 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.	

	Comprehensive	Mg/Placebo	Visit 5 Page: 5a of 6	
	Sickle Cell Centers	Toxicity Check	rage. Sa or o	
			CSCC ID:	
	Hydroxyurea & Magnesium		Carter and as [
	Pidolate (CHAMPS)		Center code:	
			Hospital code:	
	All questions relate to even	ts since the previous visit.		
Г	1) Since the last visit diarrhe	<u> </u>	sit	
Resolved Ongoing Worsened New Not present at this visit and was not present at the				
→ If new, ongoing, or worsened:				
	•			
	Grade: 1	2	uidelines for grading criteria.	
		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 abdominal 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 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 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? No change Withheld Modified			
	→ If withheld or modified, update the Mg/Placebo Study Drug Dosing Log			
	7 II withineid of modified, update the interfacebo study Drug Dostrig 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 &		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 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:

Pregnancy Test	
Not Done (C	Check reason below)
Subjec	ct male
Subjec	t has not reached menstruating age
Postme	enopausal
Hyster	ectomy
Tubal I	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: ______

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

Comprehensive Sickle Cell Centers	Interim Health History	Visit 6 Page: 1 of 6	
Hydroxyurea & Magnesium Pidolate (CHAMPS)	Date of Visit: Day Month Year	CSCC ID: Center code: Hospital code:	
All questions relate to events	s <u>since the previous study visit.</u>		
	events that led to a visit to physician's office/clinic lent 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 Care Day Day Month Year			
Date	Admitted: Date Discharged:		
Hospital Day	Month Year Day Month Ye	par ear	
Reason(s) ¹ :			
Pain crisis ²	ACS ³ Fever Ac	ute splenic sequestration	
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? ADD Yes No			
→ 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 splenic sequestration	Other complication of sickle cell 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		

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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 6 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?	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 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	Hematology Labs	Visit 6 Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
*Coll	ection Date: Day Month	Hospital code:
Labs not done → Specify:		
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 x10 ³ /mm ³ 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.
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

Visit 6

Page: 4 of 6

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

Item	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 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 Visi	t 6 Page: 4 of 6		
Hydroxyurea & Magnesium Pidolate (CHAMPS)		cscc	Center code: Hospital code:		
*C □ Labs not done → Specify:	collection Date:/ [Month Year			
TEST	VALUE				
Sodium (mmol/L)		 	IU/Placebo		
Potassium (mmol/L)		Renal Toxicity Check			
Chloride (mmol/L)		SGPT > 2x up	oper limit of normal		
CO ₂ (mmol/L)			HU/Placebo		
BUN (mg/dL)			Toxicity Check		
Creatinine (mg/dL)			L subjects < 18 years of age L subjects ≥ 18 years of age		
Calcium (mg/dL)					
SGPT/ALT (U/L)					
Alk phosphatase (U/L)			curs, <u>stop</u> the study ociated with the		
Total bilirubin (mg/dL)			oxicity.		
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	_	lacebo ty Chec		Visit	6		Pad	1e· 5	a of 6
Sickle Cell Centers	TOXICI	ly Cile	, N				· αξ		4 01 0
				cscc	ID:				
Hydroxyurea & Magnesium					,	Center	codo		
Pidolate (CHAMPS)						Center	code.		
					Н	ospital	code:		
All questions relate to events	since the previous vi	sit.							
1) Since the last visit diarrhea	nas/is: Diarrhe	ea was not	evaluated at th	is visit					
Resolved Ongoing	Worsened	New [t at this visit	and v	vas no	t prese	ent at t	he
		ı L	previous vi				,	•	
→ If new, ongoing, or w									
Grade: 1 [2 3 4	→ See Cl	RF Completion	Guidelines	s for	gradir	ng crit	eria.	
→ For all Grad	es complete AE form								
→ For Grade 3	complete SAE form if s	subject is	hospitalized						
→ For Grade 4	complete SAE form								
Duration:c	ayshours								
2) Since the last visit abdomin	al pain has/is:	Abdom	inal pain was	not evaluat	ed a	t this \	/isit		
Resolved Ongoing	Worsened	New	Not prese	nt at this visi visit	it and	was n	ot pre	sent a	t the
→ If ongoing, worsened, activities?	or new, is pain severe	enough t	o interfere with	n daily 🔲	Yes	s	ı	No	
→ If resolved or onge	oing modify AE Form as	s appropr	iate						
→ If new, add AE to A	E Form								
3) Since last visit signs of deh	ydration have/are?		ehydration wa	s not evalu	ıated	at thi	s visit		
Resolved Ongoing	Worsened	New	Not prese	ent at this vis visit	sit and	d was r	not pre	sent a	t the
→ If resolved or ongoing	modify AE Form as ap	propriate							
→ If new, add AE to AE F	orm								
4) Does/did subject meet criter	ia for Mg/Placebo tox	icity*?	Ye	s	No				
→ If yes, complete an AE F	Form.								
5) What action was taken with	5) What action was taken with Mg/Placebo? No change Withheld Modified								
→ If withheld or 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 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	Page: 5b of 6
Hydroxyurea &		CSCC ID:	
Magnesium Pidolate (CHAMPS)		Cente	er code:
		Hospita	al code:

All questions relate to events since the previous visit.

LIU/Diagoba Hanatia Taviaitu Chaek
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:

	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: ______

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.	

ţ	Comprehensive Sickle Cell Centers	Interim Health History	Visit 7 Page: 1 of 7
1	Hydroxyurea & Magnesium Pidolate (CHAMPS)	Date of Visit: Day Month Year	CSCC ID: Center code: Hospital code:
	pected Date of Next Visit:	Day Month Year	e to CHAMPS_labs@rhoworld.com
1) Ha	as the subject had <u>acute e</u> partment/day hospital/urg	since the previous study visit. events that led to a visit to physician's office/clinic ent care facility, or a hospitalization?	c/ emergency Yes No
	<u> </u>	utton and record information for each event	
Trea	atment Location: Physician's Office / Clinic	Date of Encounter: Day Month Year	
	Emergency Department / Day Hospital / Urgent Ca		
Reaso	Date Hospital Day	Admitted: Date Discharged: Month	ar
F	Pain crisis ²	ACS ³ Fever Ac	ute splenic sequestration
	Clinical stroke Other, specify	Cancer Priapism He	patic sequestration
ho		n crisis(es) at home ⁴ for which there was no y department/day hospital/urgent care visit?	Yes No ADD
-	od Transfusion?	Yes No	
)	If yes, click the "ADD" b	utton and record date and number of units or cc's for Select one:	r each transfusion.
Dat	e Transfused: Day	Month Year Number cc's	OR units/cc's unknown
Rea	ason:		_
	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 pain cri	cy 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.	r; 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:
Laurationa relata ta avanta 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:

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 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	Hematolo	gy Labs	Visit 7	Page	: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)				Center code:	
*Col	Ilection Date: Day	//	Ho	espital code:	
Labs not done → Specify:					
TEST	VAL	.UE	ELECTRO	OPHORES	IS
Hemoglobin (g/dL)		. Hb A	(%)		
Hematocrit (%)		. 🗆	— t	Not Done - Not ansfusion or <a> 10 at previous	Hb A (%)
RBC (x10 ⁶ /mm ³)				Not Done - So Hb A (%) > 10	
WBC (x10 ³ /mm ³)			HU/	/Placebo	
MCV (fl)		. 🗆 📗	Toxic IC < 1000/mm	city Check	!
MCHC (g/dL)		. Pla	atelet count < $\ge 20\% \downarrow \text{ from}$	< 75 x10 ³ /mm	3
Platelet count (x10 ³ /i	mm³)		etal Hb < 5 g/c		/dL
% Retic		. 🗆 🗕	Either % Retion put of the same	rovided.	
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 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.

Comprehens Sickle Cell Cer		C	Chemistry La	bs		Visit 7	Paç	ge: 5 of	7
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	LUE				Placebo exicity Chec	k	
Creatinine (mg/dL)		\Box	Not required						1

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

HU/Placebo Renal Toxicity Check	
PT > 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 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			
		CSCC ID:			
Hydroxyurea & Magnesium		Center code:			
Pidolate (CHAMPS)					
		Hospital code:			
All questions relate to ever	nts <u>since the previous visit</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 Gu	idelines 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	ninal pain has/is: Abdominal pain was not	evaluated at this visit			
Resolved Ongoir					
→ 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 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

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.	

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:

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:

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 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" "date part unknown" when prompted.			

	Comprehensive Sickle Cell Centers	Interim Health History	Visit 8 Page: 1 of 6			
	Hydroxyurea & Magnesium Pidolate (CHAMPS)	Date of Visit: Day Month Year	CSCC ID: Center code: Hospital code:			
	All questions relate to events since the previous study visit. 1) Has the subject had acute events that led to a visit to physician's office/clinic/ emergency Yes No department/day hospital/urgent care facility, or a hospitalization?					
	→If yes, click the "ADD" bu	utton and record information for each event				
7	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 □ ACS³ □ Fever □ Acute splenic sequestration □ Clinical stroke □ Cancer □ Priapism □ Hepatic sequestration					
L	Other, specify					
		n crisis(es) at home ⁴ for which there was no department/day hospital/urgent care visit?		Yes N	10 [·	ADD
	→ If yes, how many pain cris	es were treated at home:				
3)	Blood Transfusion?	Yes No				
	→ If yes, click the "ADD" bu	atton and record date and number of units or cc's for	each trans	fusion.		
	Date Transfused: Day	Select one: Units Number Cc's Cc's	OR	units/cc's u	nknown	
	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)					
Preparation for anesthesia Other, specify						
² A pa hosp ³ Acut ⁴ A pa abdo	oital, Emergency Department, clinic, or provide e chest syndrome is defined as a new pulmon inful crisis <u>at home</u> must be a new event, not a	ain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours r'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 steady state situation. A pain crisis at home is defined as the occurrence of p and is not explained except by sickle cell disease. Ongoing pain at home that	ezing, cough, or a	chest pain. ties, back,		ADD

Comments for page

Comprehensive Sickle Cell Centers	Physical Exam	Visit 8 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 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	Hema	tology Lab	S	Visit 8		Page	: 3 of
Hydroxyurea & Magnesium Pidolate (CHAMPS)				CSCC ID:	Center co		
*Co	llection Date:]/ 🔲		Hospital co	ode:	
Labs not done → Specify:		Day Month	Year		-		
TEST		VALUE		ELECT	ROPHO	RESI	S
Hemoglobin (g/dL)	[Hb A	A (%)			
Hematocrit (%)					Not Dor transfus ≤ 10 at	sion or	Hb A (
RBC (x10 ⁶ /mm ³)					Not Dor Hb A (%		
WBC (x10 ³ /mm ³)]			Н	IU/Place	bo	
MCV (fl)				To:	cicity Ch	neck!	
MCHC (g/dL)		□.□	PI	latelet cou b ≥ 20% ↓ f	nt < 75 x10		3
Platelet count (x10 ³ /	mm³)			otal Hb < 5			/dL
% Retic OR ARC (x10 ³ /mm ³)	[-	Either % R Use the sa	provided	l. or this :	
/ 110 (2.10 /11111)			_ ՟				

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 real 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 8	Page: 4 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)				er code:
Labs not done → Specify:	Collection Date: Day	Month Year		
TEST	VALUE			
Sodium (mmol/L)			HU/Placeb	00
Potassium (mmol/L)			Renal Toxicity	Check
Chloride (mmol/L)		HU/Placebo Renal Toxicity Check Creatinine ≥ 1.2 mg/dL subjects < 18 years of ag Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of ag		of normal
CO ₂ (mmol/L)				
BUN (mg/dL)				
Creatinine (mg/dL)				
Calcium (mg/dL)				
SGPT/ALT (U/L)				
Alk phosphatase (U/L)		If toxicity occurs, stop the s drug associated with the toxicity.		
Total bilirubin (mg/dL)				with the
Total protein (g/dL)				
Albumin (g/dL)				
LDH (U/L)		1		

^{*} 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 diarrhe	a 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	worsened:	
	Grade: 1	2 ☐ 3 ☐ 4 → See CRF Completion G	uidelines 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 not	evaluated at this visit
	Resolved Ongoin	g Worsened New Not present a previous visit	at this visit and was not present at the
	→ If ongoing, worsene activities?	ed, or new, is pain severe enough to interfere with da	aily Yes No
	→ 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 r	ot evaluated at this visit
	Resolved Ongoin	ng Worsened New Not present previous visi	at this visit and was not present at the
	→ If resolved or ongoin	ing 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 wit	h Mg/Placebo? No change Withhe	eld 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 May not be evaluated at visits with no Chemistry Panel.	
Hepatic Toxicity		
Renal Toxicity	May not be evaluated at visits with no Chemistry Panel.	

Comprehensive Sickle Cell Centers	HU/Placebo Toxicity Check	Visit 8 Page: 5b of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
		Hospital code:

All questions relate to events since the previous visit.

HU/Placebo Hepatic Toxicity Check
SGPT > 2x upper limit of normal
1) Hepatic toxicity? Hepatic toxicity was not evaluated at this visit Resolved Ongoing Worsened New Not present at this visit and was not present at the previous visit
HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age
2) Renal toxicity? Renal toxicity was not evaluated at this visit Resolved Ongoing Worsened New Not present at this visit and was not present at the previous visit
 HU/Placebo Hematologic Toxicity Check (one or more of the following) 1. ANC < 1000/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:

nancy Te	est
☐ Not D	one (Check reason below)
	Subject male
	Subject has not reached menstruating age
	Postmenopausal
I	Hysterectomy
	Tubal ligation
	Other, specify:
Date of Col	llection: Day Month Year
Type:	Serum Urine
Result:	Positive Negative

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

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:
·	s since the previous study visit. events that led to a visit to physician's office/clinic	c/ emergency Yes No
department/day hospital/ur	gent care facility, or a hospitalization? outton and record information for each event	5
Treatment Location:		
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 Ac	ute splenic sequestration
Clinical stroke	Cancer Priapism He	patic sequestration
Other, specify		
hospitalization or emergend	in crisis(es) at home ⁴ for which there was no cy department/day hospital/urgent care visit?	Yes No ADD
→ If yes, how many pain cri	ses were treated at home:	
3) Blood Transfusion?	Yes No	
→ If yes, click the "ADD" b	outton 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	Exacerbation of anemia ACS due to splenic sequestration	Other complication of sickle cell disease (CNS event, priapism, AVN)
Preparation for anesthesi	a Other, specify	
¹ Complete AE and/or SAE forms for each reason.		ADD
Emergency Department, clinic, or provider's offic	pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hourse; and is not explained except by sickle cell disease. nary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, who	s; requires a visit to a hospital,

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:

Sical 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:	Yes ² 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.

 $^{^{2}\,}$ 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.

Comprehensive Sickle Cell Centers	Hematology Labs	S Visit 9 Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code: Hospital code:
☐ Labs not done	Ilection Date: Day Month	/
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/mm³
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		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.
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		Chemistry Labs			Visit 9 Page: 4 of				
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	VALUE		
Creatinine (mg/dL)		Not required	
SGPT/ALT (U/L)		Not required	

HU/Placebo Renal Toxicity Check									
	_								

SGPT > 2x upper limit of normal

HU/Placebo **Renal Toxicity Check**

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

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

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

Comprehensive Sickle Cell Centers	Mg/Placebo Toxicity Check	Visit 9 Page: 5a of 6			
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:			
		Hospital code:			
All questions relate to 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 Ongoin	Resolved Ongoing Worsened New Not present at this visit and was not present at the previous visit				
→ If ongoing, worsene activities?	d, or new, is pain severe enough to interfere with da	ily No			
→ 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 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

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:
		F	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:

egnancy [·]	Test
	Done (Check reason below)
	Subject male
	Subject has not reached menstruating age
	Postmenopausal
	Hysterectomy
	Tubal ligation
	Other, specify:
*Date of 0	Collection: Day Month Year
Туре:	Serum Urine
Resul	t: Positive Negative

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

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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:			
1)	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					
٦	reatment Location: Physician's Office / Clinic Emergency Department /	Date of Encounter: Day Month Year				
Day Hospital / Urgent Care Date Admitted: Date Discharged: Hospital Day Month Year Day Month Year Acute splenic sequestration 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?						
	Date Transfused: Day	Select one: Units 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, specify	Other complication of sickle cell disease (CNS event, priapism, AVN)			
² A pa Eme	plete AE and/or SAE forms for each reason. 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. 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 10 Page: 2 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
	No. 11 -	Hospital code:

Il questions relate to events s				
	ince Visit 7.			
cer				
_	peen diagnosed with cancer? and complete Adverse Event an		Yes No No eent forms as appropriate.	
Date diagnosed: Day	/ Month Year			
				AD
-	undergone any neuroimaging pand record details for each type or each type of test.		Yes No	
Date of test: Day	Month Year			
	Month Year MRA CT	Cerebral angiography	Other,specify	

- 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	tance below the l	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	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	Page: 4 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
*Coll	ection Date: Day Month	Hospital code:
☐ Labs not done → Specify:		
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 x10 ³ /mm ³ Hb ≥ 20% ↓ from Visit 1
Platelet count (x10 ³ /m	nm³)	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

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	Chemistry L	Page: 5 of 8
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code: Hospital code:
*C □ Labs not done → Specify:	Collection Date: Day	Month Year
7 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, stop 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 Sickle Cell Centers	Mg/Placebo Toxicity Check	Visit 10 Page: 6a of 8		
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:		
All questions relate to events since the previous visit.				
Since the last visit diarrhe		Sit		
Resolved Ongoing				
→ If new, ongoing, or	previous visit			
Grade: 1	2 3 4 → See CRF Completion Gu	idelines for grading criteria.		
	ades complete AE form			
	• 3 complete SAE form if subject is hospitalized • 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, worsene activities?	→ 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 criteria for Mg/Placebo toxicity*?				
→ If yes, complete an AE Form.				
5) What action was taken with Mg/Placebo? No change Withheld Modified				
→ If withheld or modified, update the Mg/Placebo Study Drug Dosing Log				

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

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.

Comprehensive Sickle Cell Centers	HU/Placebo Toxicity Check	Visit 10	Page	: 6b of	f 8
Hydroxyurea &		CSCC ID:			
Magnesium Pidolate (CHAMPS)		Cente	er code:		
		Hospita	Il 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

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:
*C	Day Month Year	
Labs not do →Specify:_		
Protein (Select one, as n	eported by your lab):	
	Trace 100 200 300 1+	2+ 3+
Microscopic RBC (#/mr	n³):	
Negative C	-5 5-10 10-25 25-50	50+
Microscopic WBC (#/m	m ³):	
Negative C	-5 5-10 10-25 25-50	50+

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* 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:

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: ______.

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	Information regarding treatment at home to be determined by subject's self-report. All other pain crisis information should be obtained primarily from the medical record and secondarily by subject's self-report. Any information determined by subject self-report must be added to the medical record.
Blood Transfusions	Enter "no" if the subject has not been transfused. Enter "yes" the first time the CRF is completed following a transfusion.
Comments for page	Record general comments for this page. This comment section should not be used for comments related to data validation checks.
Unknown Date Parts	Record all known date parts. If any date part is unknown, override the query that generates in the EDC system when entering data. Supply the reason "unknown" or "date part unknown" when prompted.

	Comprehensive Sickle Cell Centers	Interim Health History	Visit 11 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	since the previous study visit. vents that led to a visit to physician's office/clinic ent care facility, or a hospitalization?	c/ emergency Yes No
	•	itton and record information for each event	
	Freatment Location: Physician's Office / Clinic	Date of Encounter: Day Month Year	
	Emergency Department / Day Hospital / Urgent Car	e Day Month Year	
	Date Hospital Day	Admitted: Date Discharged:	ar
Re	eason(s)¹:	•	
	Pain crisis ²		ute splenic sequestration
	Clinical stroke	Cancer Priapism He	patic sequestration
L	Other, specify		
	hospitalization or emergence	n crisis(es) at home ⁴ for which there was no department/day hospital/urgent care visit?	Yes No
_,		es were treated at home:	
3)	Blood Transfusion?	Yes No utton and record date and number of units or cc's for	r oach transfusion
	——————————————————————————————————————		each transiusion.
	Date Transfused: Day	Select one:	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	ergency 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 11 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 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	Hematology	/ Labs	sit 11 Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		cso	Center code:
*Co	Ilection Date: Day	Month Year	Hospital code:
☐ Labs not done → Specify:			
TEST	VALUE	ELI	ECTROPHORESIS
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 -1	Toxicity Check!
MCHC (g/dL)		Platelet	count < 75 x10³/mm³ % ↓ from Visit 1
Platelet count (x10 ³ /	mm³)		b < 5 g/dL or > 13.5 g/dL
% Retic			r % Retic <u>OR</u> ARC should be provided.
ARC (x10 ³ /mm ³)		Use t	the same unit for this subject at all study visits.

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.

						1			
Comprehens Sickle Cell Cer		C	Chemistry La	bs		Visit 11		ge: 4 of	f 6
Hydroxyurea Magnesiur Pidolate (CHAI	m					CSCC ID:	Center code		
Was a chemistry → If yes, com → If no, leave	plete this	s page.	raluation of toxicity?		Yes	s	No		
	*Colle	ection Date:	Day Month	/	ear				
TEST		VAL	.UE		HU/Placebo Renal Toxicity 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	
DT . Oversom bineit of manned	

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 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.	

Comprehensive Sickle Cell Centers	Mg/Placebo Toxicity Check	Visit 11 Page: 5a of 6
Hydroxyuroa 8		CSCC ID:
Hydroxyurea & Magnesium		Center code:
Pidolate (CHAMPS)		
All questions relate to ever	sto cinco the province visit	Hospital code:
All questions relate to ever		
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 Gu	uidelines 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 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, worsene activities?	d, or new, is pain severe enough to interfere with da	ily Yes No
→ 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 n	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 ongoin	ng 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 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 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 Page: 5b of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
, , , , , , , , , , , , , , , , , , ,		Hospital code:

All questions relate to events since the previous visit.

•
HU/Placebo Hepatic Toxicity Check
SGPT > 2x upper limit of normal
1) Hepatic toxicity? Hepatic toxicity was not evaluated at this visit Resolved Ongoing Worsened New Not present at this visit and was not present at the previous visit
HU/Placebo Renal Toxicity Check
Creatinine ≥ 1.2 mg/dL subjects < 18 years of age Creatinine ≥ 1.4 mg/dL subjects ≥ 18 years of age
2) Renal toxicity? Renal toxicity was not evaluated at this visit Resolved Ongoing Worsened New Not present at this visit and was not present at the previous visit
 HU/Placebo Hematologic Toxicity Check (one or more of the following) 1. ANC < 1000/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

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

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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 se other pain crisis information should be obtained primarily from the medical secondarily by subject's self-report. Any information determined by su 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 refor 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 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?					
	→ If yes, click the "ADD" button and record date and number of units or cc's for each transfusion. Select one: Date Transfused:					
	Reason: Exacerbation of anemia due to an aplastic crisis Exacerbation of anemia due to splenic sequestration Exacerbation of anemia due to splenic sequestration ACS Other complication of sickle cell disease (CNS event, priapism, AVN)					
² A pa Eme	Preparation for anesthesia Other, specify Complete AE and/or SAE forms for each reason. ADD ADD ADD ADD ADD ADD ADD A					

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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:

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 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	Hematology Labs			Visit 12	Page	: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)					enter code:	
*Co	llection Dat	e:]/ 🔲	Hos	spital code:	
Labs not done →Specify:		Day Month	Yea	ar		
TEST		VALUE		ELECTRO	PHORESI	s
Hemoglobin (g/dL)			Hb	A (%)]. [
Hematocrit (%)				tı	Not Done - No ransfusion or 10 at previo	Hb A (%
RBC (x10 ⁶ /mm ³)					Not Done - Su Ib A (%) > 10	
WBC (x10 ³ /mm ³)				HU/	Placebo	
MCV (fl)				Toxic ANC < 1000/mm	ity Check!	
MCHC (g/dL)			P	Platelet count < Ib ≥ 20% ↓ from	75 x10 ³ /mm ³	3
Platelet count (x10 ³ /	′mm³)			Total Hb < 5 g/d		/dL
% Retic OR ARC (x10 ³ /mm ³)				Use the same	rovided.	
1 ' '			· •			

If toxicity occurs, $\underline{\text{stop}}$ 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:
*Co ☐ Labs not done →Specify:	Ilection Date:/ [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 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 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 &		CSCC ID:		
Magnesium Pidolate (CHAMPS)		Center code:		
		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 previous visit	this visit and was not present at the		
→ If new, ongoing, or	worsened:			
Grade: 1	2 3 4 → See CRF Completion Gu	uidelines for grading criteria.		
→ For all Gr	ades complete AE form			
	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 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 wit	h Mg/Placebo? No change Withhe	ld 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 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:

Not Done (Check reasons) Subject male	TI Delowy		
Subject has not re	eached menstruating age		
Postmenopausal			
Hysterectomy			
Tubal ligation			
Other, specify:			
ate 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:

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 each location and provide all applicable dates. <u>Do not</u> click the 'ADD' button fo 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 comments field at the bottom of the page if more information about a reason the 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	s 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" bu	utton and record information for each event					
-	Freatment Location: Physician's Office / Clinic	Date of Encounter:					
	Emergency Department / Day Hospital / Urgent Car	Day Month Year Day Month Year Year					
Re	Date Admitted: Date Discharged: Date Discharged: Day Month Year Reason(s)¹:						
	Pain crisis ² ACS ³ Fever Acute splenic sequestration						
	Clinical stroke Cancer Priapism Hepatic sequestration Other, specify						
			Yes No				
٥,	-	Yes	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 ACS Other complication of sickle cell disease (CNS event, priapism, AVN)						
1 Com	Preparation for anesthesia plete AE and/or SAE forms for each reason.	Other, specify	455				
² A pa Eme	in crisis is defined here as the occurrence of pergency 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					

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 relate to events since Visit 10.	
ncer	
ince Visit 10, has this subject been diagnosed with cancer?	
→ If yes, record details below and complete Adverse Event and Serious Adverse Event forms as appropriate.	
Date diagnosed: Type:	
	ADD
euroimaging	
ince Visit 10, has this subject undergone any neuroimaging procedures? → If yes, click the ADD button and record details for each type of test. → Complete one record for each type of test.	
Date of test: Day Month Year	
Type of test¹:	
Was this result abnormal? Yes² No Equivocal³	
If yes, describe brief findings:	

- 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	nysical 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 Labs	S Visit 13 Page: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
*Coll	ection Date: Day Month	Hospital code:
Labs not done → Specify:		
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/mm³
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.
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

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.

Comprehensive Sickle Cell Centers		C	Chemistry Lab	S		Visit 13 Page: 5 of 7			7	
Hydroxyurea & Magnesium Pidolate (CHAMPS)						CSCC ID:	Center co	Γ		
Was a chemistry → If yes, com → If no, leave	plete this	s page.	valuation of toxicity?		Yes	s 🔲	No			
	*Colle	ection Date:	Day Month]/ [_Y	ear					
TEST		VAL	LUE			HU/F Renal To	Placebo xicity Ch	neck		
Creatinine (mg/dL)			Not required		SGPT	> 2x unne				

Not required

SGPT/ALT (U/L)

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 einco tho provious visit	Hospital code:	
<u> </u>			
1) Since the last visit diarrhe Resolved Ongoing	Worsened New Not present at	sit 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	ades complete AE form		
→ For Grade	→ For Grade 3 complete SAE form if subject is hospitalized		
→ For Grade	• 4 complete SAE form		
Duration:	Duration:dayshours		
2) Since the last visit abdominal 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 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 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*?			
→ 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 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? 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 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:

regnancy 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: _____

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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: Hospital code:
	Expected Date of Next Visit:	Day Month Year → Email date	e to CHAMPS_labs@rhoworld.com
Al	Il questions relate to events	since the previous study visit.	
		events that led to a visit to physician's office/clini lent care facility, or a hospitalization?	c/ emergency Yes No
	→If yes, click the "ADD" b	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 Care Day Day Month Year		
Date Admitted: Date Discharged: Hospital Day Month Year Day Month Year			
Re	eason(s)1:		
	Pain crisis ²	ACS ³ Fever Ac	ute splenic sequestration
	Clinical stroke	Cancer Priapism He	epatic sequestration
	Other, specify		
2)	Has the subject had any <u>pai</u> hospitalization or emergenc	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:	
l	Date Transfused: Day	Month Year Number units	OR units/cc's unknown
	Reason:		
Exacerbation of anemia due to an aplastic crisis Exacerbation of anemia 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 pai		pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours by office; and is not explained except by sickle cell disease.	s; requires a visit to a
		ary infiltrate on chest x-ray associated with a fever (> 38.5° C), tachypnea, who	eezing, cough, or chest pain.

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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 14 Page: 2 of 6
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 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	Hematology	<i>t</i> Labs	Visit 14 Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		C	CSCC ID: Center code: Hospital code:
Labs not done	lection Date: Day	Month Year	
TEST	VALUE	E	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!
MCHC (g/dL)	<u> </u>	Plate	< 1000/mm³ elet count < 75 x10³/mm³ 20% ↓ from Visit 1
Platelet count (x10 ³ /n	nm³)	Total	I Hb < 5 g/dL or > 13.5 g/dL
% Retic OR ARC (x10 ³ /mm ³)			ther % Retic <u>OR</u> ARC should be provided. se the same unit for this subject at all study visits.

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 Hydroxyurea & Magnesium Pidolate (CHAMPS)	Chemistry L	Page: 4 of 6 CSCC ID: Center code: Hospital code:
*Co Labs not done →Specify:	llection 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 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 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 abdom	inal 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 ongoi	i 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	E Form.	
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 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	age: 5b of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center cod	de:
,		Hospital cod	le:

All questions relate to events since the previous visit.

This questions relate to evente and provious 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:

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

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

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
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-
Blood Transfusions	report must be added to the medical record. 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:		
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	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	Day Month Year			
	Date	Admitted: Date Discharged:			
	Hospital Day	Month Year Day Month Ye	ar		
Re	eason(s) ¹ :				
L	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? es were treated at home:	Yes No		
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 Number Cc's	OR units/cc's unknown		
	Reason: Exacerbation of anemia due to an aplastic crisis Preparation for anesthesia	Exacerbation of anemia ACS Curve due to splenic sequestration Other, specify	Other complication of sickle cell disease (CNS event, priapism, AVN)		
¹ Com	plete AE and/or SAE forms for each reason.		ADD		
Eme	ergency 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, who	s; requires a visit to a hospital,		

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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:

hysical Exa	am
Not	t Done → Specify:
1) Weigh	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 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	Hematology L	abs Visit 15 Page: 3 of 6
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:
*Co	Ilection Date: /	Hospital code:
☐ Labs not done → Specify:	,	onth 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 (x10 ³ /mm ³)		Either % Retic <u>OR</u> ARC should be provided. 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

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		C	Chemistry Lab	os		Visit 15		e: 4 of	6
Hydroxyurea & Magnesium Pidolate (CHAMPS)						CSCC ID:	Center code:		
Was a chemistry → If yes, com → If no, leave	plete this	page.	valuation of toxicity?		Yes		No		
	*Colle	ction Date:	Day Month	/	ear				
TEST		VAL	.UE				Placebo exicity Check		
Creatinine (mg/dL)			Not required		SGPT	> 2x uppe	r limit of norma	al	

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

	Comprehensive Sickle Cell Centers	Mg/Placebo Toxicity Check	Visit 15	Page: 5a of 6	
	Hydroxyurea &		CSCC ID:		
	Magnesium Pidolate (CHAMPS)		Center	code:	
	Fidulate (CHAMFS)		Hospital	code:	
	All questions relate to even	ts <u>since the previous visit</u> .			
	1) Since the last visit diarrhe	a has/is: Diarrhea was not evaluated at this vis	sit		
	Resolved Ongoing		his visit and was not	present at the	
	→ If new, ongoing, or	worsened: previous visit			
	Grade: 1	2 3 4 → See CRF Completion Gu	idelines for gradin	g criteria.	
	→ For all Gr	ades complete AE form			
		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 not	evaluated at this v	isit	
	Resolved Ongoin	g Worsened New Not present at previous visit	this visit and was n	ot present at the	
	→ If ongoing, worsene activities?	d, or new, is pain severe enough to interfere with da	ily Yes [No	
	→ If resolved or on	going 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	t this visit and was n	ot 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 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 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: 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?		
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 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:

egnancy Te	one (Check reason below)
	Subject male
	Subject has not reached menstruating age
	Postmenopausal
	Hysterectomy
	Tubal ligation
	Other, specify:
*Date of Co	llection: 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: ______.

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 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 	
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 question generates in the EDC system when entering data. Supply the reason "une "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?				
Treatment Location:	utton and record information for each event Date of Encounter:			
Physician's Office / Clinic	Day Month Year			
Emergency Department / Day Hospital / Urgent Ca				
Date Hospital Day	Admitted: Date Discharged: Month	ar		
Reason(s) ¹ :				
Pain crisis ²	ACS ³ Fever Acc	ute splenic sequestration		
Clinical stroke	Cancer Priapism He	patic sequestration		
Other, specify				
2) Has the subject had any <u>pain crisis(es) at home⁴</u> 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?				
3) Blood Transfusion?				
Select one:				
Date Transfused: Day Month Year Number Day 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 due to splenic sequestration ACS Other complication of sickle cell disease (CNS event, priapism, AVN)				
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.

Comprehensive Sickle Cell Centers	Interim Health History	Visit 16 Page: 2 of 7
Hydroxyurea &		CSCC ID:
Magnesium Pidolate (CHAMPS)		Center code:
		Hospital code:

Visit 13, has this	subject been diagnosed with cancer	?	Yes No	
If yes, record details	s below and complete Adverse Event a	nd Serious Adverse I	Event forms as appropriate.	
Date diagnosed:	Day Month Year			
				Α
	subject undergone any neuroimaging		Yes No)
e Visit 13, has this a lif yes, click the ADE	button and record details for each test		Yes No	0
e Visit 13, has this solid lift yes, click the ADE	button and record details for each test		Yes No	
e Visit 13, has this a lif yes, click the ADE Date of test: Da Type of test ¹ :	button and record details for each test	t/type.	Other,specify	

- 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:

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?
	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

Visit 16

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	y Labs	sit 16 Page: 4 of 7
Hydroxyurea & Magnesium 'idolate (CHAMPS)		CSC	CC ID: Center code:
*Col	llection Date: Day	Month Year	Hospital code:
☐ Labs not done → Specify:			
TEST	VALU	E ELI	ECTROPHORESIS
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)		Platelet	t count < 75 x10³/mm³)% ↓ from Visit 1
Platelet count (x10 ³ /r	mm³)		b < 5 g/dL or > 13.5 g/dL
% Retic	<u> </u>		r % Retic <u>OR</u> ARC should be provided.
OR ARC (x10 ³ /mm ³)		Use t	the same unit for this subject at all study visits.
ANC (x10 ³ /mm ³)			

If toxicity occurs, 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	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	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	_	Placebo	C	Visit 16	Pa	ge: 6a	of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)				CSCC ID:	Center cod	de:	
				Н	ospital cod	le:	
All questions relate to even	ts since the previous	<u>visit</u> .					
1) Since the last visit diarrhe	a has/is: Dia	rhea was not e	evaluated at this vis	sit			
Resolved Ongoing	Worsened	New	Not present at the previous visit	his visit and w	vas not pro	esent at t	he
→ If new, ongoing, or	worsened:						
Grade: 1	2 3 4	→ See CR	F Completion Gu	idelines for (grading d	riteria.	
→ For all Gr	ades complete AE form)					
→ For Grade	3 complete SAE form	if subject is h	ospitalized				
→ For Grade	• 4 complete SAE form						
Duration:	_dayshours	3					
2) Since the last visit abdom	inal pain has/is:	Abdomi	nal pain was not e	evaluated at	this visit		
Resolved Ongoin	g Worsened	New	Not present at previous visit	this visit and	was not p	resent at	the
→ If ongoing, worsene activities?	d, or new, is pain seve	re enough to	interfere with dai	ly Yes		No	
→ If resolved or or	going modify AE Form	as appropria	te				
→ If new , add AE to	AE Form						
3) Since last visit signs of de	ehydration have/are?	☐ De	hydration was no	ot evaluated	at this vi	sit	
Resolved Ongoin	ng Worsened	New	Not present at previous visit	t this visit and	l was not p	oresent a	t the
→ If resolved or ongoi → If new, add AE to AE		appropriate					
4) Does/did subject meet cri	teria for Mg/Placebo to	oxicity*?	Yes	No No			
→ If yes, complete an AE	Form.						
5) What action was taken wit	h Mg/Placebo?	No change	Withhel	d \square M	odified		

→ 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: ______.

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 <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.

	0	Interim Health History	Early Termination		
	Comprehensive Sickle Cell Centers	internii Healtii History	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	s 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		
		utton and record information for each event			
1	reatment Location:	Date of Encounter:			
	Physician's Office / Clinic	Day Month Year			
	Emergency Department / Day Hospital / Urgent Car	re Day Month Year			
	Data	Admitted: Date Discharged:			
	Hospital Day	Month Year Day Month Ye	ar		
Re	ason(s)¹:	24,	<u></u>		
	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? 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: Month Year 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			
	plete AE and/or SAE forms for each reason.	pain in the extremities, back, abdomen, chest, or head that lasts at least 2 hours	ADD		
Eme	rgency Department, clinic, or provider's office	and in not explained except by sickle cell disease. ary 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	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:

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?
	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	Hematolo	gy Labs	Early Termination Page: 4 of 7
Hydroxyurea & Magnesium Pidolate (CHAMPS)			CSCC ID: Center code:
*Co	Ilection Date:	//	Hospital code:
☐ Labs not done → Specify:	·		
TEST	VAL	.UE	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!
MCHC (g/dL)			ANC < $1000/\text{mm}^3$ Platelet count < $75 \times 10^3/\text{mm}^3$ Hb $\geq 20\% \downarrow \text{ from Visit 1}$
Platelet count (x10 ³ /	/mm³)		Fotal 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.

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 &		CSCC ID:
Magnesium 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? 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 \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 reason the lab was not done.	

Comprehensive Sickle Cell Centers	Urinalysis	Early Termination Page: 7 of 7
Hydroxyurea & Magnesium		CSCC ID: Center code:
Pidolate (CHAMPS)		Hospital code:
*C	Day Month Year	
☐ Labs not do		
Protein (Select one, as n	eported by your lab):	
Negative 1	Trace 100 200 300 1+	2+ 3+
Microscopic RBC (#/mr	n³):	
Negative (-5 5-10 10-25 25-50	50+
Microscopic WBC (#/m	m ³):	
Negative 0	-5 <u> </u>	<u> </u>

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

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	cicity V		Page	e: 1 of	4
Hydroxyurea & Magnesium Pidolate (CHAMPS)				csc	C ID:	enter c	ode:		T T
					Hos	spital c	ode:		$\underline{\mathbb{I}}$
Was a hematology lab co → If yes, complete this → If no, leave the rema	page.			Yes		No			
*Col	lection Da	te: Day Month	/ [Year					
TEST		VALUE		ELE	CTRC	РНО	RES	is	
Hemoglobin (g/dL)			ŀ	Hb A (%)].[
Hematocrit (%)					tı	ransfu	sion o	lo recen r Hb A (ous visit	(%
RBC (x10 ⁶ /mm ³)						Not Do Hb A (9		suspect 0	
WBC (x10 ³ /mm ³)					HU/	Place	ebo		
MCV (fl)				ANC < 1	Toxic	ity C		!	
MCHC (g/dL)				Platelet Hb > 209	count <	75 x1		n ³	
Platelet count (x10 ³ /i	mm³)			Total Hb < 5 g/dL or > 13.5 g/dL					
% Retic		□.□			•	ovide	d.		
OR ARC (x10 ³ /mm ³)				Use th	he same at all	unit fo		subject	
ANC (x10 ³ /mm ³)									
collection date differs from the	ne visit date	for this visit, explain:							

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

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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.

Comprehens Sickle Cell Cer		C	Chemistry La	bs		Toxicity		e: 2 of	4
Hydroxyurea Magnesiur Pidolate (CHAI	n					CSCC ID:	Center code:		
Was a chemistry lab conducted for evaluation of toxicity? → If yes, complete this page. → If no, leave the remainder of the page blank.									
	*Colle	ction Date:	Day Month	/	ear				
TEST		VAL	.UE				Placebo xicity Check		
Creatinine (mg/dL)		$\Box_{-}\Box$	Not required						

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

HU/Placebo Renal Toxicity Check						
 _			٠.	,		

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	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? 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

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

Ongoing

- HU/Placebo Study Drug Dosing Log
- Mg/Placebo Study Drug Dosing Log
- HU/Placebo Study Drug Record
- Mg/Placebo Study Drug Record
- AE for Painful Crisis
- Study Completion
- Concomitant Medications
- AE Not for Painful Crisis
- Protocol Deviation Form

^{*} Only the forms associated with the toxicity are required.

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		CSCC ID: Center code:			
Pidolate (CHAMPS)		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

Mg/Placebo Study Drug Dosing Log

Ongoing

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

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

Initial Dose:

Dose	Dose (B.I.D.)	Start Date	Stop Date	
(mEq/kg B.I.D.)	(mL)	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		
		/	/		
		//	//		
		/	/		
		//	//		
		//	//		
		//	//		
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		/	/		
		/	/		
		//	/		
		I	ADD		

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						
Hydroxyurea & Randomization Number: Magnesium Pidolate (CHAMPS)			CSCC ID:			Denter code: Despital			
		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 · mg	200 mg 500 mg				Day Month Year
Unscheduled					200 mg 500 mg				Day Month Year
									n must correspond to the or this dispensing date.
Comments									

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

ADD

Mg/Placebo Study Drug Record

Ongoing

CSCC Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF COMPLETION GUIDELINES

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

Comprehensive Sickle Cell Centers		Mg/Placebo					
SICKIE	e Cell Centers		Study Drug	Record			
Live	luesa a e				CSCC ID:		Center code:
	Iroxyurea & esium Pidolate				<u> </u>		-
	CHAMPS)						Hospital code:
`	,						
		Dispens	e			Retur	n
Visit # (drop-down)	Start Date	Not Dispensed	Bottle Number	Prescribed Dose (B.I.D.)	Return Volume	Not Returned	Return Date
		1			fl. oz.		
OR	Day Month Year			mL		ГП	Day Month Year
Unscheduled	•				_		Day Month Fear
Oriscinculicu							
					fl. oz.		
					mL		Day Month Year
					fl. oz.		
					□ mL		Day Month Year
				NOTE: Return Infor	mation must	correspond to the bottle	
				number recorded fo			
Comments							

ADD

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				
	Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code: Hospital code:				
Co	mplete this form for each	pain event.					
١	Was this a Serious Adverse	Event?	ubmit an SAE report to SDMC?				
	Date of onset:	/ / Date of resolution:	Day Month Year				
	Location of Pain (Check a Chest Back	## that apply) Abdomen Leg(s) Arm(s) Head & Neck					
7	Type of Pain Typical Atyp	ical					
What was the outcome? (Check one) Resolved without sequelae Resolved with sequelae Ongoing Present at death, not contributing to death Death due to this AE What was the level of severity? (Check one) Mild - Home Moderate - ER Severe - Hospital							
١	What was the relationship to	study drug(s)? (Check one)					
		Probably not Possibly related Probelated / Prob	ably related Definitely related				
٧	Vhat action was taken?	(Check all that apply)					
	No Action	Concomitant Medication Giver	١				
	Study Treatment Into	errupted ER/Day Hospital					
	Study Treatment Discontinued Hospitalization						
	Study Treatment Dose Adjusted						
4	As a result of this AE, was the subject transfused? ☐ Yes ☐ No → If yes, complete the transfusion section of the Interim Health History form.						
Did the pain event evolve into another adverse event?							
	→ If yes, complete an Adverse Event form and specify Adverse Event.						
	Adverse Event, spe	ecify					

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	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 participation in the s	opinion the subject's health, safety and/or well-being study	was threatened by continued				
Subject was nonadh	nerent. Specify:					
Subject lost to follow	v-up					
Subject or subject's	legal representative requested to withdraw.					
Specify:		<u> </u>				
Discontinuation (c	heck all that apply)					
Decline in Hb le	evel to < 5 g/dL					
Increase in Hb	level to > 13.5 g/dL (viscosity concerns)					
Initiation of chronic transfusion						
Hepatic dysfunction (SGPT > 2x upper limit of normal)						
Renal toxicity (creatinine ≥ 1.2 mg/dL if age < 18 years, creatinine ≥ 1.4 mg/dL if age ≥ 18 years)						
Pregnancy						
Stroke						
Pulmonary failure requiring intubation Grade 3 or 4 toxicity lasting longer than two weeks						
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 these questions were not asked, indicate the reason they were not asked.			
PI Signature	The Principal Investigator's signature is required to show that he/she has reviewed the data entries within this CRF and, to the best of his/her knowledge, the data represent a complete and accurate record of the subject's participation in the study.			
Signature Date	The PI signature and date of the PI's signature is required.			

Comprehensive Sickle Cell Centers	Study Completion	Page: 3 of 3							
Hydroxyurea & Magnesium Pidolate (CHAMPS)		CSCC ID: Center code:							
Tidolato (OTIZIIII O)		Hospital code:							
Subject: Ask this question if the Subject is at least 14 years of age; skip to "Parent/Guardian" if the Subject is <14. Note that you will also ask this question of the Parent/Guardian for all Subjects under that age of 18.									
In your opinion, into which	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	•								
Specify:	Not asked, other reason:								
Parent/Guardian: Ask this	question if the Subject is less than 18 years of ag	е.							
Hydroxyurea & Ma	gnesium. If marked:								
• •	t the subject to continue using Hydroxyurea? Ye	s No Don't know							
→ Would you wan	t the subject to continue using Magnesium? $\qquad \qquad$ Ye	s No Don't know							
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	ebo & Magnesium Placebo								
☐ No opinion									
Not asked, subject ≥ 18 years old									
Not asked, parent/guardian was not present at this visit									
Not asked, other reason:									
Specify:									
Investigator's Statement:									
	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							

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 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

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		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 Day Month	Year Year	N No Y Yes				
2	N No Y Yes	Day Month Day Month	Year Year	N No Y Yes				
3	N No Y Yes	Day Month Day Month	Year Year	N No Y Yes				
4	N No Y Yes	Day Month Day Month	Year Year	N No Y Yes				
	1 OUTCOME 1 = Resolved with 2 = Resolved with 3 = Medically stal 4 = Present at de	n sequelae	² SEVERIT 1 = Mild 2 = Moder 3 = Severe 4 = Life-th	ate e reatening	³ RELATIONSHII 1 = Unrelated 2 = Probably not/remote 3 = Possibly rela	1 = N0 $2 = St$ $3 = St$ $4 = C0$	ION TAKEN one udy treatment interr udy treatment disco	ntinued on given/chang

- 5 = Death
- 6 = Ongoing

- 5 = Fatal
- 4 = Probably related 5 = Definitely related

- 5 = Hospitalization 6 = ER/Day hospital 7 = Other, specify

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: / / / / / / / / / / / / / / / / / / /	CSCC ID: Center	code:
		Form Completed by:	Hospital	code:
	Complete a separate forn	for each deviation from the protocol.		
d	Pate of protocol deviation or ate when deviation was iscovered:	Was the subject F	Randomized?	No Yes
	Type of Deviation:	Day Month Year		
	1. Randomization or Mas	king Error, Specify:		
	2. Dosing Error, Specify:			
_	Did this lead to an over	dose? No Yes		
	3. Missed Visit, Record th			
	Why was the visit mis	sed?		
	Caregiver wa	as ill		
	Transportation	on problems		
	Scheduling of	difficulties		
	Subject expe	erienced AE requiring hospitalization		
	Subject expe	erienced AE requiring visit to Clinic or Physician's office	ce	
	Subject expe	erienced AE requiring Emergency Dept/Day Hospital/	Urgent Care visit	
	Subject expe	erienced AE not requiring medical attention		
	Other, specif			
	· 	ue to AE, be sure to complete AE & SAE forms as app	oropriate.)	
L	4. Mistimed Visit, Record	the Visit Number:		
	Did the visit occur too	early or too late? Too early Too	late	
_	_	sit window was the visit? days		
	_	r Laboratory Measure, Record the Visit Number:		
	Was the entire asses	sment mistimea?		
	No: Which p	part 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			
		part 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 Deviation (continued)		Ong	going	Page 1b of 1
Hydroxyurea & Magnesium Pidolate (CHAMPS)			csco	Cent	er code:
				Hospita	al code:
7. Inclusion Criteria Not Inclusion Number	Met				. (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 Devia	iion:			
Did this deviation result in		☐ No			plete AE form.)
→ If yes, was the AE	serious? No Yes	(If yes, compl	lete SAE forr	n.)	
Will the subject continue	with the study?	No No	Yes	(If no, comp	lete discontinuation form.
Is report to IRB required f	or this deviation?	No No	Yes		
→ If yes, Date reported:	Day Month Year				
If further action is require	d, describe it:				
Additional Comments:					