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The Use of Novel Therapies to Reconstitute Blood Cell Production and Promote Organ Performance, Using Bone Marrow Failure as a Model

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This protocol has been accruing subjects appropriately. During this report year 27 subjects were consented; 20 were enrolled; 6 were deemed 'screen failures', and 1 was withdrawn prior to enrollment. Of the 6 screen failures, 1 subject was found to have taken leucine over-the-counter; 1 was not chronically transfusion dependent as per the criteria of the study; 1 had a history of severe non-compliance; 1 had elevated liver function tests beyond the limits allowed on the study; 1 was found to be on Prednisone on review; and 1 was being treated for pancreatic insufficiency and was deemed ineligible as the absorption of the study drug with pancreatic enzyme replacement is unknown. Three subjects (02-003, 02-004, and 02-005) required re-consenting as their enrollment did not occur within 30 days of the signing of the original consent. There were no severe adverse events reported during this study period. Please see the list of study activities below:

15. SUBJECT TERMS

Nothing listed

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INTRODUCTION: Diamond Blackfan anemia (DBA) is a rare inherited red cell aplasia. Mutations have been described in ribosomal protein genes. Currently standard therapy includes corticosteroids, red cell transfusions or stem cell transplantation; however all are fraught with numerous side effects. Leucine is one of the branched chain amino acids and has been shown to upregulate protein translation. This is a pilot study to test the feasibility of administering leucine to 50 patients with DBA, monitoring for clinical hematologic response and side effects.

BODY: This protocol has been accruing subjects appropriately during this reporting period. During this report year 27 subjects were consented. Of these, 20 were enrolled; 6 were deemed 'screen failures', and 1 was withdrawn prior to enrollment. Of the 6 screen failures, 1 subject (01-014) was found to have taken leucine over-the-counter; 1 subject (01-015) was not chronically transfusion dependent as per the criteria of the study; 1 subject (02-002) had a history of severe non-compliance; 1 had elevated liver function tests beyond the limits allowed on the study; 1 subject (02-007) was found to be on Prednisone on review; and 1 subject (02-006) was being treated for pancreatic insufficiency and was deemed ineligible as the absorption of the study drug with pancreatic enzyme replacement is unknown. Three subjects (02-003, 02-004, and 02-005) required reconsenting as their enrollment did not occur within 30 days of the signing of the original consent.

Of the 38 total consented subjects, 26 subjects were enrolled, 7 are 'screen failures', 4 are pending enrollment, and 1 subject withdrew prior to enrollment.

During the study period 14 patients started study drug; 9 subjects completed treatment; 1 subject withdrew by parental decision prior to starting study drug; and 13 subjects are still receiving study drug. Four patients will start drug in the next period once they clear their enrollment.

One subject (05-002) remains transfusion free as of 22AUG14.

No toxicity has been noted and there were no severe adverse events reported during this study period.

There are 11 institutions with IRB approval for this study. The University of Arkansas (Little Rock, AK) is still pending IRB and DOD approvals. Memorial Health University Medical Center (Savannah, GA) has IRB approval and is pending submission to the DOD.

KEY RESEARCH ACCOMPLISHMENTS:
There are no key research accomplishments to date as the study is still accruing subjects.

REPORTABLE OUTCOMES:
There are no reportable outcomes to date as the study is still accruing subjects.

CONCLUSION:
There are no results to report at this time, however there are no untoward toxicities reported amongst the subjects and one subject is transfusion-free since starting the study drug.

REFERENCES:
There are no references to report at this time.

APPENDICES:
There are 2 appendices: Table 1 is an enrollment log of all the subjects and Table 2 is a list of all the study sites.

SUPPORTING DATA:
There are no supporting data.

Table 1

Enrollment Log 2014

Site ID	Subject ID	Consent Date	Reconsent if not within 30 days of start of enrollment	Enroll Date	Evaluable? (Y/N)	Reason unevaluable	Date Completed/ Unevaluable	Treatment Period Started	Treatment Period Ended	Withdrawn (Y/N)
01	01-002	17-Jun-13	N/A	27-Jun-13	Y	N/A	26-Mar-14	27-Jun-13	26-Mar-14	N
01	01-003	17-Jun-13	N/A	28-Jun-13	Y	N/A	24-Mar-14	8-Jul-13	24-Mar-14	N
01	01-001	17-Jun-13	N/A	17-Jun-13	Y	N/A	25-Sep-13	15-Jul-13	13-Aug-13	Y
01	01-004	22-Jun-13	N/A	5-Jul-13	Y	N/A	25-Mar-14	12-Jul-13	25-Mar-14	N
01	01-005	26-Jun-13	N/A	28-Jun-13	Y	N/A	31-Mar-14	10-Jul-13	31-Mar-14	N
01	01-006	28-Jun-13	N/A	13-Aug-13	Y	N/A	19-Sep-13	21-Aug-13	17-Sep-13	Y
01	01-007	16-Jul-13	N/A	16-Jul-13	Y	N/A	30-May-14	12-Sep-13	30-May-14	N
01	01-008	19-Jul-13	N/A	29-Jul-13	Y	N/A	1-Jun-14	16-Aug-13	1-Jun-14	N
01	01-009	29-Jul-13	N/A	29-Jul-13	Y	N/A	12-May-14	16-Aug-13	12-May-14	N
01	01-010	29-Jul-13	N/A	29-Jul-13	Y	N/A	12-May-14	16-Aug-13	12-May-14	N
01	01-011	2-Aug-13	N/A	N/A	N	Screen Failure	N/A	N/A	N/A	Y
01	01-012	5-Nov-13	N/A	12-Nov-13	Y	N/A	19-Aug-14	21-Nov-13	19-Aug-14	N
01	01-013	18-Dec-13	N/A	18-Dec-13	N	Parental Decision	N/A	N/A	N/A	Y
01	01-014	19-Dec-13	N/A	N/A	N	Screen Failure	N/A	N/A	N/A	Y
01	01-015	30-Dec-13	N/A	N/A	N	Screen Failure	N/A	N/A	N/A	Y
02	02-001	7-Feb-14	N/A	11-Mar-14	Y	N/A	ongoing	11-Mar-14	ongoing	N
02	02-002	7-Feb-14	N/A	N/A	N	Screen Failure	20-Mar-14	N/A	N/A	Y
01	01-016	9-Feb-14	N/A	12-Mar-14	Y	N/A	ongoing	21-Mar-14	ongoing	N
01	01-017	9-Feb-14	N/A	12-Mar-14	Y	N/A	ongoing	21-Mar-14	ongoing	N
03	03-001	26-Mar-14	N/A	3-Apr-14	Y	N/A	ongoing	17-Apr-14	ongoing	N
04	04-001	3-Apr-14	N/A	4-Apr-14	Y	N/A	ongoing	10-Apr-14	ongoing	N
03	03-002	21-Apr-14	N/A	28-Apr-14	Y	N/A	ongoing	19-May-14	ongoing	N
05	05-001	28-Apr-14	N/A	N/A	N	Screen Failure	N/A	N/A	N/A	Y
02	02-005	5-May-14	18-Sep-14	pending	Y	N/A	N/A	pending	N/A	N
04	04-002	9-May-14	N/A	16-May-14	Y	N/A	ongoing	13-May-14	ongoing	N
05	05-002	9-May-14	N/A	13-May-14	Y	N/A	ongoing	23-May-14	ongoing	N
02	02-007	12-May-14	N/A	N/A	N	Screen Failure	N/A	N/A	N/A	Y
02	02-003	19-May-14	24-Sep-14	pending	Y	N/A	N/A	pending	N/A	N
02	02-004	21-May-14	20-Sep-14	pending	Y	Withdrawn early	N/A	pending	N/A	Y
02	02-006	21-Jun-14	N/A	N/A	N	Screen Failure	N/A	N/A	N/A	Y
07	07-001	24-Jun-14	N/A	27-Jun-14	Y	N/A	ongoing	1-Jul-14	ongoing	N
06	06-001	1-Jul-14	N/A	11-Jul-14	Y	N/A	ongoing	22-Jul-14	ongoing	N
06	06-002	5-Aug-14	N/A	3-Sep-14	Y	N/A	ongoing	23-Sep-14	ongoing	N
06	06-003	5-Aug-14	N/A	3-Sep-14	Y	N/A	ongoing	23-Sep-14	ongoing	N
08	08-001	12-Aug-14	N/A	8-Sep-14	Y	N/A	N/A	pending	N/A	N
09	09-001	2-Sep-14	N/A	12-Sep-14	Y	N/A	ongoing	17-Sep-14	ongoing	N
01	01-018	5-Sep-14	Withdrawn	Withdrawn	N	Withdrawn	N/A	N/A	N/A	Y
11	11-001	19-Sep-14	N/A	pending	Y	N/A	N/A	pending	N/A	N

Table 2. Study Sites

Subsite Listing	DOD reference #	Local IRB Protocol #	Site PI	Site Coordinator
01-Feinstein Institute for Medical Research (Manhasset, NY)	A-16175.a	12-375B	Adrianna Vlachos, MD	Eva Atsidaftos
02-Stanford University (Stanford, CA)	A-16175.b	IRB-27253	Bertil Glader, MD, PhD	Heather Hilmoe
03-Children's Hospital of Philadelphia (Philadelphia, PA)	A-16175.c	IRB-13-010091	Helge Hartung, MD	Peter Nicholas
04-University of Michigan Health System (Ann Arbor, MI)	A-16175.d	HUM00080618	Kelly Walkovich, MD	Ashley Shaver
05-University of Texas Southwestern (Dallas, TX)	A-16175.e	STU032013-081	Zora R. Rogers, MD	Leah Adix
06-Children's Hospital Boston (Boston, MA)	A-16175.f	IRB-P00009112	Colin A. Sieff, MD	Krystle Benedict
07- Riley Hospital for Children (Indianapolis, IN)	A-16175.g	IRB-1312051728 | N	Grzegorz Nalepa, MD	Shannon Maraldo, CCRP
08-Phoenix Children's Hospital (Phoenix, AZ)	A-16175.h	IRB-13-105	Sanjay Shah, MD	Erica Olson, RN
09-University of Missouri (Columbia, MO)	A-16175.i	IRB-1209323	Thomas W. Lowe, MD	Kim Ebersol
10-Memorial Health University Medical Center (Savannah, GA)	withdrawn	closed	Martin Johnston, MD	Yvetta Lee
11-University of Louisville (Louisville, KY)	A-16175.k	IRB-14.0268	Arun Panagrahi, MD	April Loveall/ Kayla Bowling
12-Children's Specialty Center of Nevada (Las Vegas, NV)	A-16175.j	WIRB -20140525	Waseem Alhushki, MD	Daniel Crosier
13- University of Arkansas (Little Rock, AK)	pending	pending	Jason Farrar, MD	Jason Farrar, MD

10OCT2013 Subsite b. – Stanford University – received IRB approval for study
14OCT2013 Subsite f. – Boston Children's Hospital – received IRB approval for study
05NOV2013 Subject ID 01-012 consented
25NOV2013 Subsite e. – University of Texas Southwestern Medical Center – received IRB approval for study
18DEC2013 Subject ID 01-013 consented
19DEC2013 Subsite h. – Phoenix Children's Hospital – received IRB approval for study and study amendment
19DEC2013 Subject ID 01-014 consented
30DEC2013 Subject ID 01-015 consented
03JAN2014 Subsite d. – University of Michigan – received IRB approval for study
22JAN2014 Subsite i. – University of Missouri-Columbia – received IRB approval for study
28JAN2014 Subsite d. – University of Michigan – received IRB approval for study amendment
07FEB2014 Subject ID 02-001 consented
07FEB2014 Subject ID 02-002 consented
09FEB2014 Subject ID 01-016 consented
09FEB2014 Subject ID 01-017 consented
11FEB2014 Subsite g. – Indiana University – received IRB approval for study
04MAR2014 Subsite – Memorial Health University Medical Center – received IRB approval for study
26MAR2014 Subject ID 03-001 consented
03APR2014 Subject ID 04-001 consented
08APR2014 Subsite j. – Children's Specialty Center of Nevada – received IRB approval for study
17APR2014 Subsite k. – University of Louisville – received IRB approval for study
21APR2014 Subject ID 03-002 consented
28APR2014 Subject ID 05-001 consented
05MAY2014 Subject ID 02-005 consented
09MAY2014 Subject ID 04-002 consented
09MAY2014 Subject ID 05-002 consented
12MAY2014 Subject ID 02-007 consented
19MAY2014 Subject ID 02-003 consented
21MAY2014 Subject ID 02-004 consented
21JUN2014 Subject ID 02-006 consented
24JUN2014 Subject ID 07-001 consented
01JUL2014 Subject ID 06-001 consented
08JUL2014 Subsite c. – Children's Hospital of Philadelphia – received IRB renewal for study
05AUG2014 Subject ID 06-002 consented
05AUG2014 Subject ID 06-003 consented
12AUG2014 Subject ID 08-001 consented
02SEP2014 Subject ID 09-001 consented
05SEP2014 Subject ID 01-018 consented
18SEP2014 Subject ID 02-005 reconsented as enrollment did not occur within 30 days of original consent
19SEP2014 Subject ID 11-001 consented
20SEP2014 Subject ID 02-004 reconsented as enrollment did not occur within 30 days of original consent
24SEP2014 Subject ID 02-003 reconsented as enrollment did not occur within 30 days of original consent