Clinical Pharmacology
& Biopharmaceutics

Research Article Open Access

L-Glutamine Therapy Reduces Hospitalization for Sickle Cell Anemia and Sickle β°-Thalassemia Patients at Six Months – A Phase II Randomized Trial

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on NAD redox potential. e results were intriguing in that in every patient, NAD redox potential essentially normalized with reduction in subjective clinical symptoms [18,20]. In addition, there was a decrease in permanently sickled cells in the peripheral smear of room air incubated venous blood. Figure 1a* and 1b* illustrate the di erence following 12 weeks of L-glutamine therapy. In another pilot study, we found a major decrease in endothelial adhesion rates when compared to controls [25-27]. ese ndings supported the rationale to design and conduct a multi-center phase II proof of concept clinical trial to examine L-glutamine therapy in comparison to placebo in sickle cell anemia patients.

*Data on le

Material and Methods

is research was carried out according to the principles of the Declaration of Helsinki and in compliance with good clinical practice (GCP) and other applicable regulatory requirements. e study protocol was approved by the Institutional Review Boards (IRBs) of all participating sites: [1] Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California; [2] e Cancer Institute of New Jersey, New Brunswick, New Jersey; [3] Kaiser Permanente, Bell ower, California; and [4] Grady Memorial Hospital, Atlanta, Georgia. Signed informed consent or assent was obtained prior to the initiation of the patient in the study. is included discussion on the risks and/or discomforts that may be experienced by participants. is clinical trial was registered at http://www.clinicaltrials.gov. (Identi er: NCT00125788).

Criteria for eligibility were: at least 5 years of age; diagnosed with sickle cell anemia or sickle °-thalassemia as documented by hemoglobin electrophoresis; had at least 2 episodes of painful crises within 12 months of the screening visit, if treated with an anti-sickling agent within 3 months of the screening visit, the therapy must have been continuous for at least 3 months with the intent to continue for

Study medication dosing

L-glutamine or Placebo was provided as a powder that was mixed with beverage or food immediately before ingestion orally twice a day. e dosage was based on body weight (0.3 grams per kilogram per dose) and was adjusted in increments of 5 grams with an upper limit of 30 g/day. Patients were given verbal instructions for self-administration of the study medication and written instructions were also included on the consent form. Patients were instructed that the study drug should be taken between 6 am and 9 am and again between 6 pm and 9 pm. ey were also instructed to mix the powder immediately before ingestion with water or any non-heated beverage other than alcohol or with any non-heated food such as yogurt, applesauce, or cereal.

A er 48 weeks of treatment the dose was gradually tapered to zero over 3 weeks to minimize the possibility of sudden onset of a sickle cell crisis. For patients who withdrew early from the study before Week 48, the 3-week tapering period was started at the time of withdrawal (unless the reason for the withdrawal was that the patient had not taken any study medication over the previous study interval or was pregnant). ose patients returned for an early withdrawal (nal) visit 2 weeks a er completion of tapering.

Data processing and statistical analysis

Criteria for Evaluation:

E cacy: e primary e cacy endpoint was the number of painful sickle cell crises through Week 48 and prior to the start of taper. A painful sickle cell crisis was de ned as a visit to a medical facility that lasted more than 4 hours for acute sickling-related pain that was treated with a parenterally administered narcotic (except for facilities in which only orally administered narcotics were used). Secondary e cacy variables were number of hospitalizations for sickle cell pain at Week 24 and 48, number of emergency room visits for sickle cell pain at Week 24 and 48, days usual activities were interrupted due to sickle cell pain, height, weight, growth curve (<18 years of age), hematologic parameters, narcotic usage, alcohol and tobacco use, pain level, energy level, activity level, appetite, subjective exercise tolerance, subject quality of life (RAND 36-item Health Survey and Peds QL Pediatric Quality of Life Questionnaires).

Safety: Safety analyses were performed on the safety population with no imputation of missing values. Safety endpoints include incidence of adverse events (AEs), serious adverse events (SAEs), clinical laboratory results, and vital signs.

Statistical Methods:

Populations: e safety population included all patients who received at least one dose of study medication (N = 70). e full analysis dataset included all patients who received at least one dose of study medication and had been diagnosed with sickle cell anemia or sickle °-thalassemia documented by hemoglobin electrophoresis and had at least 2 episodes of painful crises within 12 months prior to the screening visit (N = 62). Table 1 describes the Safety Population and other dataset pro les.

e treatment groups were compared with respect to the number of painful sickle cell crises, number of hospitalizations, and number of emergency room visits using a Cochran-Mantel-Haenszel test. is non-parametric method was used due to the unanticipated number of non-completers resulting in a substantial proportion of imputed data. e data were not normally distributed and there was no suitable transformation. Two imputation methods were used. For discontinued

	N
Enrolled	
6LWH 6XEMHFWV ([FOXGHG	
Safety Population Dataset	
)DLOHG ([FOXVLRQ ,QFOXVLRQ	8
)XOO $QDO\VLV 'DWDVHW	62

2I¿FLDO WHUPLQDWLRQ RI 6LWH E\ (PPDXV RQ misconduct

7ZR SDWLHQWV GLG QRW KDYH WKH FRUUHFW G PLQLPXP RI FULVHV LQ WKH ODVW PRQWKV

Table 1: Safety population was used for safety analysis and the full analysis dataset ZDV XVHG IRU HI¿FDF\ DQDO\VLV

patients with less than 85 days on treatment, the number of crises, hospitalizations, and emergency room visits were imputed by the mean number for the completed patients of the same treatment group. For discontinued patients with 85 days or longer on treatment, the number of crises, hospitalizations, and emergency room visits at week 48 were imputed by patient according to their individual rate at the date of withdrawal. All imputed values were rounded up to the nearest whole integer.

Results

Between April 23, 2004 and May 29, 2008, 81 patients were enrolled at ve centers. Of these patients, data for a total of 19 patients were not included (due to reasons described in Statistical Methods above) for a total of 62 evaluable patients (Full Analysis Dataset) from four centers. Baseline characteristics between groups were comparable. e mean age was 30.5 and 26.5 years in the L-glutamine and placebo groups respectively, with an overall range from 9 to 58 years. Six patients were under 18 years of age. e majority of patients in the L-glutamine group were female (66.7%) while the majority in the placebo group was male (65.5%). In both groups, most patients were African American and had a diagnosis of sickle cell anemia (93.9 and 82.8% respectively). Table summarizes the patient baseline demographics for the Phase II Study.

E cacy

E cacy sample size was N = 62 (Full Analysis Dataset). For the primary e cacy parameter, the mean number of painful crises was 2.5 and 5.5 for L-glutamine and placebo groups respectively at Week 24 (p = 0.060). e mean number of painful crises was 4.5 in the L-glutamine group and 10.8 in the placebo group through Week 48 (p = 0.076). Table 3 shows the mean number of events and SD for the associated groups for the primary endpoint.

For secondary endpoints, the mean number of hospitalizations for sickle cell pain was 0.8 in the L-glutamine group and 1.3 in the placebo group through Week 24 (p = 0.036). e mean number of hospitalizations through Week 48 was 1.5 in the L-glutamine group and 2.3 in the placebo group (p = 0.072). Table 4 shows the mean number of hospitalizations and SD for the associated groups for the secondary endpoint. e mean number of emergency room visits for sickle cell pain was 3.7 in the L-glutamine group and 9.4 in the placebo group through Week 24 (p = 0.105) and 1.9 and 4.7 respectively through Week 48 (p = 0.129).

ere were no notable changes in height or weight in either group or in alcohol or tobacco usage, although the majority of patients did not use either substance. Energy level tended to increase in both groups and there were no statistically signi cant between-group di erences. A higher proportion of patients in the placebo group than the L-glutamine group had above average activity levels at Week 16