ORIGINAL ARTICLE

A Phase 3 Trial of L-Glutamine in Sickle Cell Disease

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ABSTRACT

BACKGROUND

Oxidative stress contributes to the complex pathophysiology of sickle cell disease. Oral therapy with pharmaceutical-grade L-glutamine (USAN, glutamine) has been shown to increase the proportion of the reduced form of nicotinamide adenine dinucleotides in sickle cell erythrocytes, which probably reduces oxidative stress and could result in fewer episodes of sickle cell–related pain.

METHODS

In a multicenter, randomized, placebo-controlled, double-blind, phase 3 trial, we tested the efficacy of pharmaceutical-grade L-glutamine (0.3 g per kilogram of body weight per dose) administered twice daily by mouth, as compared with placebo, in reducing the incidence of pain crises among patients with sickle cell anemia or sickle β^0-thalassemia and a history of two or more pain crises during the previous year. Patients who were receiving hydroxyurea at a dose that had been stable for at least 3 months before screening continued that therapy through the 48-week treatment period.

RESULTS

A total of 230 patients (age range, 5 to 58 years; 53.9% female) were randomly assigned, in a 2:1 ratio, to receive L-glutamine (152 patients) or placebo (78 patients). The patients in the L-glutamine group had significantly fewer pain crises than those in the placebo group (P=0.005), with a median of 3.0 in the L-glutamine group and 4.0 in the placebo group. Fewer hospitalizations occurred in the L-glutamine group than in the placebo group (P=0.005), with a median of 2.0 in the L-glutamine group and 3.0 in the placebo group. Two thirds of the patients in both trial groups received concomitant hydroxyurea. Low-grade nausea, noncardiac chest pain, fatigue, and musculoskeletal pain occurred more frequently in the L-glutamine group than in the placebo group.

CONCLUSIONS

Among children and adults with sickle cell anemia, the median number of pain crises over 48 weeks was lower among those who received oral therapy with L-glutamine, administered alone or with hydroxyurea, than among those who received placebo, with or without hydroxyurea. (Funded by Emmaus Medical; ClinicalTrials.gov number, NCT01179217.)

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*A complete list of the participating institutions and investigators in the Phase 3 Trial of L-Glutamine in Sickle Cell Disease is provided in the Supplementary Appendix, available at NEJM.org.

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Oxidative stress contributes to the complex pathophysiology of sickle cell disease.[1-3] Nicotinamide adenine dinucleotide (NAD^+) is a ubiquitous oxidation–reduction (redox) cofactor in red cells. NAD^+ and its reduced form, NADH, play major roles in maintaining redox balance. Sickle red cells have a lower redox ratio ([NADH]:[NAD^++NADH]) than normal red cells.[4,5]

The amino acid L-glutamine (USAN, glutamine), a conditionally essential amino acid (i.e., one for which increased levels are needed in certain conditions, such as stress), is required to synthesize NAD. Uptake of L-glutamine is several times greater in sickle red cells than in normal red cells,[6] primarily to increase the total intracellular NAD level.[7] Oral administration of pharmaceutical-grade L-glutamine was shown to raise the NAD redox ratio within sickle cells and was associated with patient-reported clinical improvement.[8] Furthermore, in a study examining adhesion of sickle red cells to human umbilical vein endothelial cells, sickle red cells in five patients who had been treated with L-glutamine for at least 4 weeks adhered significantly less than did sickle red cells in an untreated control patient.[9] Disease severity and erythrocyte adherence to endothelium are strongly correlated[10]; thus, higher L-glutamine consumption by oxidation-stressed sickle red cells may be abetted by oral administration of L-glutamine. A 48-week randomized, placebo-controlled, phase 2 trial that compared L-glutamine with placebo showed that treatment with L-glutamine resulted in lower (although nonsignificantly lower) mean numbers of acute pain crises and hospitalizations than placebo, without causing a higher rate of toxic effects.[11] These results prompted this phase 3 trial to confirm the findings; preliminary results were reported previously.[12]

METHODS

TRIAL DESIGN AND PATIENTS

We conducted a year-long randomized, placebo-controlled, double-blind, parallel-group trial at 31 sites across the United States. The trial was approved by the appropriate institutional review boards, and written informed consent or assent was obtained from the patients or guardians as applicable.

Patients were eligible for enrollment if they were at least 5 years of age, had received a diagnosis of sickle cell anemia (homozygous hemoglobin S [HbSS]) or sickle β^0-thalassemia (HbSβ^0-thalassemia), and had had at least two pain crises (no upper limit) documented during the previous year; a pain crisis was defined as pain leading to treatment with a parenterally administered narcotic or ketorolac in an emergency department (ED) (or outpatient treatment center) or during hospitalization. Patients who were receiving treatment with hydroxyurea at a dose that had been stable for at least 3 months before screening and who intended to continue that treatment were eligible to participate. Women of childbearing potential agreed to use contraception during the study. Patients were excluded if they had been hospitalized for a reason not related to sickle cell disease within 2 months before screening, had a prothrombin-time international normalized ratio higher than 2.0, had a serum albumin level of less than 3.0 g per deciliter, had received any blood products within 3 weeks before screening, had clinically significant renal or liver disease, or had received treatment with L-glutamine within 30 days before the screening.

TRIAL PROCEDURES

Eligible patients were randomly assigned, in a 2:1 ratio, to receive pharmaceutical-grade L-glutamine or placebo, with randomization stratified according to region of participating site and status with respect to hydroxyurea use. The planned treatment period was 48 weeks, during which patients received L-glutamine powder or placebo powder (100% maltodextrin), administered orally twice daily at approximately 0.3 g per kilogram of body weight per dose (10 g, 20 g, or 30 g [maximum dose] per day), followed by a tapering period of 3 weeks and an observation period of 2 weeks (total trial duration, 53 weeks). Earlier studies of glutamine dosing in adults showed that a change in redox ratio ([NADH]:[NAD+NADH]) was consistently attained at a dose of 30 g per day.[8] The trial medication and placebo were provided in individual, visually identical packets containing 5 g of white unflavored powder, and all packets were returned by the patients for assessment of adherence. The contents of the packet were mixed with a nonheated drink or food and consumed immediately. Patients were contacted by telephone every week between

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monthly visits to encourage adherence. The validity of the trial-group assignment and the correct supply of L-glutamine or placebo for each patient were confirmed by an independent investigational drug service. Patients could receive blood transfusions and other clinically indicated treatments as needed.

END POINTS

The primary efficacy end point was the number of pain crises through week 48. Acute chest syndrome, priapism, and splenic sequestration were classified as sickle cell–related events regardless of the need for narcotics or ketorolac. Secondary efficacy end points included the number of hospitalizations for sickle cell–related pain, the number of visits to an ED (or outpatient treatment center) for sickle cell–related pain, and changes in hematologic measures (hemoglobin and hematocrit levels and reticulocyte count) from baseline through week 48. A visit to an ED (or outpatient treatment center) on the same calendar day as a hospital admission was counted only as a hospitalization.

ADJUDICATION OF PAIN CRISIS AND LABORATORY TESTS

All reported pain crises were recorded on case-report forms by investigators. An independent adjudication committee consisting of three hematology–oncology physicians who were unaware of the trial-group assignments evaluated each episode to determine whether the event met the definition of a pain crisis for the efficacy evaluation.

Coagulation screening, hemoglobin electrophoresis, human immunodeficiency virus tests, and pregnancy tests were performed, and the findings were evaluated at screening. Blood samples were obtained at screening and at the end of the study for serum chemical testing and at monthly trial visits for complete blood counts with reticulocyte counts; no dose adjustments based on results of laboratory tests were required by the protocol. NAD and NADH levels in red cells were not measured.

SAFETY MONITORING

Safety assessments began at screening and continued on a monthly basis until week 53 and included a physical examination, complete blood count, assessment for adverse events, and collection of information regarding concomitant medications and ED visits and hospitalizations. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 12.0. All serious adverse events that occurred from the time of the first dose of the trial medication or placebo (first visit of the first participant) to the end of the trial (last visit of the last participant) were reviewed by a designated independent medical monitor.

A serious adverse event was defined as any adverse event, occurring while the patient was receiving the trial medication or placebo at any dose, that resulted in death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or clinically significant disability or incapacity, or a congenital anomaly or birth defect. Notable medical events that might not have resulted in death, been life-threatening, or required hospitalization could be considered serious adverse events if it was determined, on the basis of appropriate medical judgment, that they could place the patient's health in jeopardy and might require medical or surgical intervention to prevent one of the outcomes listed in the definition of serious adverse events.

TRIAL OVERSIGHT

Academic authors and authors employed by the sponsor (Emmaus Medical) were jointly responsible for the design of the trial. The trial protocol, available with the full text of this article at NEJM.org, was prepared by employees of the sponsor, and a clinical research organization (ClinDatrix) collected the data. The data were analyzed by staff at the biostatistics division of MMS Holdings. The first draft was written by the corresponding author, and subsequent drafts were written and reviewed by all the authors; all the authors participated in the decision to submit the manuscript for publication. No one who was not an author participated in writing the manuscript. The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol and statistical analysis plan (available with the protocol at NEJM.org).

STATISTICAL ANALYSIS

Efficacy analyses were performed on data from all patients who underwent randomization, ac-

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cording to the group to which they had been assigned (intention-to-treat population) and with stratification according to region of participating site and status with respect to hydroxyurea use. The sample size was calculated with the use of the Wilcoxon rank-sum test for ordered categories and nQuery Advisor software, version 7.0 (Statistical Solutions). The primary end-point analysis was a two-sided comparison at an overall alpha level of 0.045 (adjusted for a single interim analysis). Secondary efficacy end points in the final analysis (ED visits and hospitalization) and all other end points in the final analyses were tested at the 0.05 significance level without adjustment for multiplicity. To be consistent with the method for calculating sample size, and because pain crises are not normally distributed, a nonparametric analysis of the primary end point (Cochran–Mantel–Haenszel test with the use of modified ridit scores, which is equivalent to a stratified Wilcoxon rank-sum test) was performed.[13] The Cochran–Mantel–Haenszel test compared the standardized ranks within strata (modified ridit scores) of the number of pain crises over 48 weeks between the trial groups. Because the Cochran–Mantel–Haenszel test provides P values but not an estimate of treatment effect, descriptive means and medians are presented to give context. For the patients who discontinued the trial medication or placebo, the number of pain crises was imputed as either the mean number of crises (rounded to the nearest integer) in patients in the same trial group who completed the trial or the actual number of crises the patient had at the time of discontinuation, whichever was greater. Secondary end points were analyzed by the method described for the primary end point, except that hematologic measures were analyzed with a repeated-measures analysis-of-variance model. The safety population included all patients who received at least one dose of trial medication or placebo, and safety measures, including adverse events, were analyzed descriptively.

Several additional analyses were performed. An analysis of recurrent pain crises over time was performed to estimate the mean cumulative number of pain crises over 48 weeks in each trial group and to generate a rate ratio for this variable (i.e., "intensity rate ratio," which is the ratio of the recurrent event rates in each trial group) for an estimate of the effect size[14]; we created a plot in which the mean cumulative number of pain crises according to trial group was plotted against time. We performed prespecified subgroup analyses according to hydroxyurea use, sex, and age using the negative binomial regression model to generate an estimate of the treatment effect (rate ratios) and to provide an assessment of the interaction between trial-group assignment and the subgroup variable. The time to the first pain crisis and time to the second pain crisis were plotted separately according to trial group by means of the Kaplan–Meier method, and the log-rank test was used to calculate P values. The hazard ratio with 95% confidence intervals was estimated with a Cox regression model. The proportional-hazards assumptions of the Cox model were assessed with the use of Schoenfeld residuals.[15] The 50% quartile (median) of the curve and the 95% confidence intervals were reported according to trial group. The number of occurrences of acute chest syndrome before the tapering period was evaluated by the same statistical method used for the primary end point. The cumulative numbers of days in the hospital were compared between the two trial groups with the use of the Wilcoxon rank-sum test. Analyses and tabulations were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENT CHARACTERISTICS AND DISPOSITION

The intention-to-treat population included 230 patients who were enrolled at participating sites across the United States from June 2010 through December 2013. After enrollment, two patients in the L-glutamine group were found to have sickle β^+-thalassemia (HbSβ^+); one of these patients did not receive the trial medication or placebo. Patients ranged in age from 5 to 58 years, and 53.9% were female. A total of 152 patients were randomly assigned to the L-glutamine group, and 78 to the placebo group (Table 1). Two thirds of the patients in both trial groups received concomitant hydroxyurea.

A total of 156 patients completed the trial: 97 of 152 patients (63.8%) in the L-glutamine group and 59 of 78 patients (75.6%) in the placebo group. The reasons for discontinuation were similar in the two trial groups; the most common reasons were withdrawal of consent, "other"

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Table 1. Baseline Characteristics in the Intention-to-Treat Population.*

Characteristic	L-Glutamine (N=152)	Placebo (N=78)
Age — yr		
Mean	22.4±12.32	21.4±12.42
Median (range)	19.0 (5 to 57)	17.0 (5 to 58)
Age group — no. (%)		
5–12 yr	34 (22.4)	17(21.8)
13–18 yr	41 (27.0)	26 (33.3)
>18 yr	77 (50.7)	35 (44.9)
Hydroxyurea use — no. (%)	101 (66.4)	52 (66.7)
Sex — no. (%)		
Male	73 (48.0)	33 (42.3)
Female	79 (52. 0)	45 (57.7)
Race or ethnic group — no. (%)†		
Black	144 (94.7)	73 (93.6)
Hispanic	4 (2.6)	3 (3.8)
Other	4 (2.6)	2 (2.6)
Diagnosis — no. (%)		
Sickle cell anemia	136 (89.5)	71 (91.0)
Sickle β^0-thalassemia	14 (9.2)	7 (9.0)
Sickle β^+-thalassemia	2 (1.3)	0
Sickle cell pain crises in the year before trial entry — no. (%)		
0–1	1 (0.7)	1 (1.3)
2–5	128 (84.2)	61 (78.2)
6–9	15 (9.9)	14 (17.9)
≥10	8 (5.3)	2 (2.6)
Hemoglobin level at baseline — g/dl	8.8±1.4	8.7±1.2
Hematocrit level at baseline — %	27.7±4.4	27.5±3.6
No. of reticulocytes at baseline — per mm^3	284,000±129,000	295,000±142,000

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.
† Race and ethnic group were reported by the patients.

reasons, and nonadherence (Fig. S2 in the Supplementary Appendix, available at NEJM.org).

END POINTS

Fewer pain crises occurred in the L-glutamine group than in the placebo group (P=0.005 by the Cochran–Mantel–Haenszel test), with a median of 3.0 in the L-glutamine group and 4.0 in the placebo group — a 25% difference; in addition, fewer hospitalizations occurred in the L-glutamine group than in the placebo group (P=0.005 by the Cochran–Mantel–Haenszel test), with a median of 2.0 in the L-glutamine group and 3.0 in the placebo group — a 33% difference. The number of ED visits that did not result in hospitalization did not differ significantly between the trial groups (P=0.09 by the Cochran–Mantel–Haenszel test), with a median of one visit in each group. There were no significant between-group differences in the change in hemoglobin level, hematocrit level, or reticulocyte count.

An analysis of recurrent sickle cell–related pain crises over time yielded an intensity rate ratio of 0.75 (95% confidence interval [CI], 0.62

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to 0.90, according to the Andersen–Gill model, or 95% CI, 0.55 to 1.01, according to the Lin–Wei–Yang–Ying modification of the Andersen–Gill model), which suggests that the cumulative number of pain crises was 25% lower in the L-glutamine group than in the placebo group over the entire 48-week treatment period (Fig. 1). Furthermore, the median time to the first pain crisis was 84 days (95% CI, 62 to 109) in the L-glutamine group, as compared with 54 days (95% CI, 31 to 73) in the placebo group (hazard ratio, 0.69; 95% CI, 0.52 to 0.93; P=0.02) (Fig. 2A), and the median time to the second pain crisis was 212 days (95% CI, 153 to 250) in the L-glutamine group, as compared with 133 days (95% CI, 115 to 179) in the placebo group (hazard ratio, 0.68; 95% CI, 0.49 to 0.96; P=0.03) (Fig. 2B). No significant violations of the proportional-hazards assumptions were detected (P≥0.70 for all) (see the Supplementary Appendix). There were significantly fewer occurrences of acute chest syndrome in the L-glutamine group than in the placebo group; 13 of 152 patients (8.6%) in the L-glutamine group had at least one episode of acute chest syndrome, as compared with 18 of 78 (23.1%) in the placebo group (P=0.003 by the Cochran–Mantel–Haenszel test) (Table 2). The median cumulative number of days in the hospital were 6.5 (range, 0 to 94) in the L-glutamine group and 11 (range, 0 to 187) in the placebo group (P=0.02).

In the subgroup analysis according to sex, the treatment effect was similar in male patients (rate ratio, 0.73; 95% CI, 0.51 to 1.05) and female patients (rate ratio, 0.81; 95% CI, 0.59 to 1.12), with no significant interaction between trial-group assignment and sex (P=0.68). The negative binomial regression analysis according to age generated rate ratios for pain crisis of 0.64 (95% CI, 0.45 to 0.89) among the patients older than 18 years of age and 0.93 (95% CI, 0.67 to 1.29) among those 18 years of age or younger, with no significant interaction between trial-group assignment and age (P=0.12). The subgroup analysis according to hydroxyurea use showed a consistent treatment effect across hydroxyurea use subgroups, with a rate ratio of 0.77 (95% CI, 0.58 to 1.03) in the group that used hydroxyurea and 0.78 (95% CI, 0.51 to 1.20) in the group that did not use hydroxyurea. No significant interaction between trial-group assignment and hydroxyurea use was observed (P=0.96) (Fig. S1 in the Supplementary Appendix). Mean corpuscular volumes were consistent throughout the trial in both groups and were higher in the patients who received concomitant hydroxyurea, which suggests that these patients followed their prescribed hydroxyurea regimen (Table S1 in the Supplementary Appendix). Adherence, as determined according to the median percentage of trial medication or placebo taken, was similar in the two trial groups (77.4% in the L-glutamine group and 76.6% in the placebo group).

SAFETY

The rate of adverse events was higher in the placebo group than in the L-glutamine group (100% vs. 98.0%), as was the rate of serious adverse events (87.1% vs. 78.2%). Adverse events with a higher incidence in the L-glutamine group than in the placebo group and with at least a 5% incidence in the L-glutamine group are listed in Table 3; adverse events for which the between-

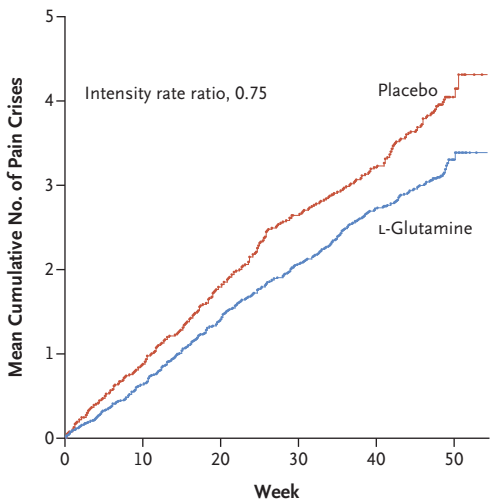

Figure 1. Recurrent Events of Sickle Cell–Related Pain Crisis over Time, According to Trial Group.

An analysis of sickle cell–related pain crisis over time yielded an intensity rate ratio (i.e., the ratio of the recurrent event rates in each trial group) of 0.75 (95% CI, 0.62 to 0.90, according to the Andersen–Gill model; and 95% CI, 0.55 to 1.01, according to the Lin–Wei–Yang–Ying modification of the Andersen–Gill model), which indicates that the cumulative number of painful crises was 25% lower in the L-glutamine group than in the placebo group over the entire 48-week treatment period.

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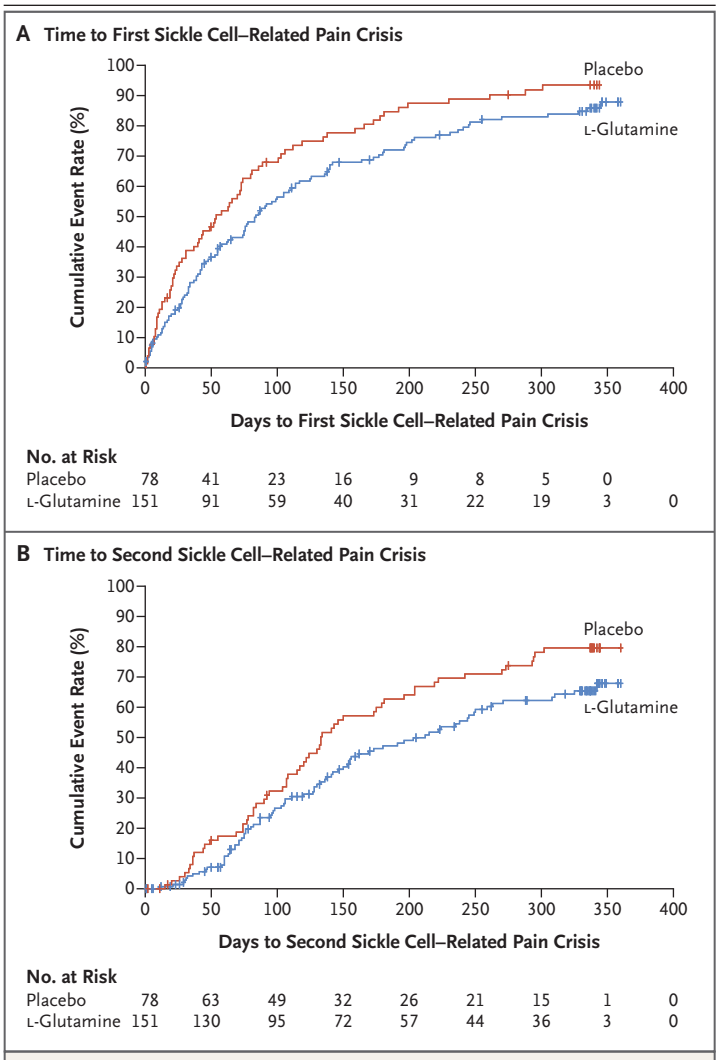

Figure 2. Time to Sickle Cell–Related Pain Crisis.

Panel A shows the Kaplan–Meier curves for time to the first sickle cell–related pain crisis. The median time to the first pain crisis was 84 days (95% CI, 62 to 109) in the L-glutamine group, as compared with 54 days (95% CI, 31 to 73) in the placebo group (hazard ratio, 0.69; 95% CI, 0.52 to 0.93; P=0.02). Panel B shows the Kaplan–Meier curves for time to the second sickle cell–related pain crisis. The median time to the second pain crisis was 212 days (95% CI, 153 to 250) in the L-glutamine group, as compared with 133 days (95% CI, 115 to 179) in the placebo group (hazard ratio, 0.68; 95% CI, 0.49 to 0.96; P=0.03).

group difference in incidence was greater than 5 percentage points included nausea, arm or leg pain, and back pain. Two patients in the L-glutamine group, both in their mid-40s, died during the trial. The cause of death in both cases was sudden cardiac death; both patients had a long history of organ failure and coexisting medical conditions (Fig. S3 in the Supplementary Appendix). A review article that addressed concerns about the long-term use of L-glutamine suggested that there are possible adverse effects but did not cite adverse cardiac effects.[16] Five patients in the L-glutamine group withdrew early because of adverse events (hypersplenism and abdominal pain [one patient], dyspepsia [one]; a burning sensation in the feet [one]; hot flashes [one]; and pregnancy [one]). Two additional pregnancies occurred during the trial in the L-glutamine group; both women were withdrawn from the trial, and the reason for withdrawal was categorized as "other." The outcome of the three pregnancies is unknown; however, no reports of adverse outcomes were reported at the investigational sites.

DISCUSSION

In the current trial, in which the majority of patients received concomitant hydroxyurea, the number of pain crises per patient was significantly lower in the L-glutamine group than in the placebo group and differed between trial groups by a median of one event over 48 weeks. The time to the first pain crisis began to diverge within 2 weeks after the start of the treatment period, with sustained separation of curves over the duration of the trial. The analysis of recurrent pain crises over time reinforced the observation that over the entire trial period, the median number of pain crises was 25% lower with L-glutamine than with placebo (Fig. 1). The exact mechanisms by which L-glutamine reduces the frequency of pain crises have not been fully elucidated.

Acute chest syndrome is the second most common cause for hospitalization and a leading cause of death among patients with sickle cell disease.[17] Although the total number of episodes of acute chest syndrome was relatively small, there were significantly fewer episodes in the L-glutamine group than in the placebo group. Acute chest syndrome is associated with higher tricuspid regurgitant jet velocity, a biomarker of hemolytic rate and pulmonary hypertension[18,19] that correlates strongly with low erythrocyte glutamine levels.[3]

The 33% between-group difference in the median number of hospitalizations is notable because hospitalization can be very costly. The mean

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Table 2. End-Point and Additional Analyses.

Through Week 48	L-Glutamine (N=152)	Placebo (N=78)	P Value
Primary end point			
No. of pain crises			0.005*
Mean	3.2±2.24	3.9±2.54	
Median (range)	3 (0–15)	4 (0–15)	
Secondary end points			
No. of hospitalizations for sickle cell–related pain			0.005*
Mean	2.3±1.99	3.0±2.33	
Median (range)	2 (0–14)	3 (0–13)	
Cumulative no. of days in hospital			0.02†
Mean	12.1±16.6	18.1± 27.4	
Median (range)	6.5 (0–94)	11 (0–187)	
No. of emergency department visits for sickle cell–related pain			0.09*
Mean	1.1±1.49	1.5±2.29	
Median (range)	1 (0–12)	1 (0–15)	
Additional analyses			
Median no. of days to first pain crisis (95% CI)	84 (62–109)	54 (31–73)	0.02‡
Median no. of days to second pain crisis (95% CI)	212 (153–250)	133 (115–179)	0.03‡
Episodes of acute chest syndrome — no. (%)			0.003*
0	139 (91.4)	60 (76.9)	
≥1	13 (8.6)	18 (23.1)	
1	10 (6.6)	13 (16.7)	
2	3 (2.0)	4 (5.1)	
3	0	1 (1.3)	

* The P value was calculated with the use of the Cochran–Mantel–Haenszel test with modified ridit scores, with adjustment for region and hydroxyurea use
† The P value was calculated with the use of the Wilcoxon rank-sum test.
‡ The P value was calculated with the use of the log-rank test of the Kaplan–Meier survival curve.

number of ED visits was lower in the L-glutamine group than in the placebo group, but the difference was not significant.

Hydroxyurea was approved in 1998 by the Food and Drug Administration (FDA) for the treatment of adults with sickle cell disease after the Multicenter Study on Hydroxyurea showed that the annualized median number of pain crises was lower, by two pain crises, among the patients who received hydroxyurea than among those who received placebo.[20] In our study, the majority of patients were already receiving hydroxyurea therapy before enrollment and yet met the trial requirement of having had two or more pain crises in the previous year. Mean corpuscular volume, a sensitive indicator of hydroxyurea therapy in sickle cell anemia, was higher among the patients receiving concomitant hydroxyurea and was stable throughout the trial, which indicates that the patients probably adhered to their prescribed hydroxyurea therapy. A subgroup analysis according to hydroxyurea use indicated that the benefits of L-glutamine therapy were consistent regardless of whether the patients were receiving hydroxyurea. Subgroup analyses showed no sex-related or age-related differences in response to L-glutamine therapy.

Not all the patients were able to complete the

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Table 3. Adverse Events (Safety Population).*

Adverse Event	L-Glutamine (N=151)	Placebo (N=78)
	no. of patients (%)	
Cardiac disorders		
Tachycardia	8 (5.3)	4 (5.1)
Gastrointestinal disorders		
Constipation	38 (25.2)	19 (24.4)
Nausea	34 (22.5)	13 (16.7)
Vomiting	22 (14.6)	10 (12.8)
Abdominal pain upper	16 (10.6)	6 (7.7)
Diarrhea	12 (7.9)	5 (6.4)
General disorders and administration site conditions		
Chest pain (noncardiac)	21 (13.9)	7 (9.0)
Fatigue	9 (6.0)	1 (1.3)
Infections and infestations		
Urinary tract infection	10 (6.6)	3 (3.8)
Musculoskeletal and connective tissue disorders		
Pain in extremity	24 (15.9)	6 (7.7)
Back pain	20 (13.2)	5 (6.4)
Nervous system disorders		
Headache	32 (21.2)	14 (17.9)
Dizziness	8 (5.3)	4 (5.1)
Respiratory, thoracic, and mediastinal disorders		
Nasal congestion	11 (7.3)	5 (6.4)

* The table shows adverse events with a higher incidence in the L-glutamine group than in the placebo group and with at least a 5% incidence in the L-glutamine group. Adverse events are categorized by system organ class and preferred terms according to the *Medical Dictionary for Regulatory Activities*, version 12.0.

study, but the reasons for early withdrawal were mainly unrelated to the trial medication or placebo; although the percentage of patients who withdrew early was higher in the L-glutamine group than in the placebo group, the reasons for withdrawal were similar in the two groups. Recruitment and retention in a year-long study is difficult in an already burdened population,[21] and the overall noncompletion rate of 32% was similar to that in a recent multicenter trial of crizanlizumab in patients with sickle cell disease (35%).[22]

A pharmacokinetic study published in 2010[23] corroborated earlier reports of successful oral administration of the powder formulation of L-glutamine.[24-26] Our study used a pharmacologic-based dose of L-glutamine that did not exceed a literature-based "safe" maximum daily dose of L-glutamine in humans.[8,25] Patients with renal and hepatic insufficiencies were not included in the current trial.

The benefits of hydroxyurea therapy are well documented and substantial in all age groups, and therapy should be offered to nearly all patients with sickle cell anemia.[27] However, hydroxyurea is underused on account of both real and perceived risks,[28] and frequent monitoring of blood counts to evaluate both toxic effects and therapeutic benefit is cumbersome. Our analysis of mean corpuscular volume showed a persistent elevation among the patients who received concomitant hydroxyurea, an indication of ongoing adherence to hydroxyurea therapy; this finding suggests that the effect of L-glutamine may be additive. L-Glutamine thus provides an alternative therapy for those who decline treatment with hydroxyurea or who may have unacceptable side effects from hydroxyurea, as well as an additive therapy to lower the incidence of pain crises for those who may have suboptimal response to hydroxyurea.

Our trial showed that the median number of pain crises over 48 weeks was lower among the patients who received L-glutamine than among those who received placebo, regardless of hydroxyurea use; the rates of nausea, noncardiac chest pain, fatigue, and musculoskeletal pain were higher with L-glutamine than with placebo. On the basis of the results of this phase 3 trial, the FDA granted approval of pharmaceutical grade L-glutamine (Endari, Emmaus Medical) as a prescription drug to reduce the rate of acute complications of sickle cell disease among adults and children 5 years of age and older.

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