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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

JOINT CLINICAL AND STATISTICAL REVIEW

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Established Name	L-glutamine
(Proposed) Trade Name	Endari
Therapeutic Class	Amino acid
Applicant	Emmaus Medical, Inc.
Formulation(s)	Oral Powder: 5 g of L-glutamine powder per paper-foil-plastic laminate packet
Dosing Regimen	0.3g/kg body weight, maximum dose 30g/day
Indication	For the treatment of sickle cell disease

Note: For the purposes of this review, “Endari” refers to the drug under review, “NutreStore (L-glutamine powder for oral solution)” refers to formulations stated to comply with the USP monograph, and “glutamine” refers to any therapeutic glutamine, including those of unknown provenance.

Table of Contents

JOINT CLINICAL AND STATISTICAL REVIEW	1
TABLE OF CONTENTS	2
TABLE OF TABLES	4
TABLE OF FIGURES	6
TABLE OF ABBREVIATIONS.....	7
1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	9
1.1. Recommendation on Regulatory Action	9
1.2. Basis of the Recommendation	9
2 INTRODUCTION AND REGULATORY BACKGROUND	17
2.1. Product Information	17
2.2. Currently Available Treatments for Proposed Indication	18
2.3. Availability of Proposed Active Ingredient in the United States	18
2.4. Important Issues with Consideration to Related Drugs	18
2.5. Summary of Pre-submission Regulatory Activity Related to Submission.....	18
2.6. Other Relevant Background Information	19
2.7. Compliance with the Pediatric Research Equity Act	19
3 ETHICS AND GOOD CLINICAL PRACTICES	20
3.1. Submission Quality and Integrity	20
3.2. Compliance with Good Clinical Practices.....	21
3.3. Financial Disclosures	23
4 SIGNIFICANT ISSUES RELATED TO OTHER REVIEW DISCIPLINES	23
4.1. Chemistry Manufacturing and Controls	23
4.2. Preclinical Pharmacology/Toxicology	23
4.3. Clinical Pharmacology	24
4.4. Interdisciplinary Review Team (IRT)	26
4.5. Pharmacovigilance	26
5 SOURCES OF CLINICAL DATA	27
5.1. Tables of Clinical Studies as listed by the Applicant in Module 5.2	27
5.2. Review Strategy	27
5.3. Discussion of Individual Studies/Clinical Trials	28
5.3.1. Study GLUSCC09-01:	28
5.3.2. Study 10478	32
5.3.3. Legacy Studies	36
6 REVIEW OF EFFICACY	38
6.1. Methods	38

Clinical Review

NDA 208587

Endari® (L-glutamine)

6.1.1.	Trial Design and Endpoints	38
6.1.2.	Statistical Analysis Plan	39
6.2.	Study Population	42
6.3.	Results	45
6.4.	Statistical Issues	56
6.5.	Conclusions and Recommendations	57
7	REVIEW OF SAFETY	58
7.1.	Methods	58
7.2.	Adequacy of Safety Assessments	60
7.3.	Major Safety Results	62
7.3.1.	Deaths	62
7.3.2.	Nonfatal Serious Adverse Events	66
7.3.3.	Dropouts and/or Discontinuations	69
7.3.4.	Significant Adverse Events	70
7.4.	Supportive Safety Results	71
7.4.1.	Common Adverse Events	71
7.5.	Other Safety Explorations	83
7.5.1.	Dose Dependency for Adverse Events	83
7.5.2.	Time Dependency for Adverse Events	85
7.5.3.	Drug-Demographic Interactions	85
7.5.4.	Drug-Disease Interactions	92
7.5.5.	Drug-Drug Interactions	93
7.6.	Additional Safety Evaluations	93
7.6.1.	Human Carcinogenicity	93
7.6.2.	Human Reproduction and Pregnancy Data	93
7.6.3.	Pediatrics and Assessment of Effects on Growth	93
7.6.4.	Overdose, Drug Abuse Potential, Withdrawal and Rebound	94
7.6.5.	Hepatotoxicity	94
7.7.	Additional Safety Issues	95
7.7.1.	Literature Review	95
7.7.2.	Other literature reports	102
8	POST-MARKET EXPERIENCE	103
9	APPENDICES	103
9.1.	Advisory Committee Meeting	103
9.2.	Labeling Recommendations	104
9.3.	References	105

Table of Tables

Table 1: Benefit-Risk Framework	9
Table 2: NDA Submission and Amendments.....	20
Table 3: Table Clinical Trials	27
Table 4: Study GLUSCC09-01 treatment dosage schedule	29
Table 5: GLISCC09-01 - Study Schedule of Assessments	30
Table 6: Summary of Protocol Amendments	32
Table 7: Study 10478 treatment dosage schedule	34
Table 8: Baseline Demographic and Clinical Characteristics by Study and Treatment Group.....	43
Table 9: Patient Disposition, by Study and Treatment Group.....	44
Table 10: Patients remaining (N) on study by 12-week intervals and Days on study, by study and treatment group.....	44
Table 11: Primary Efficacy Analysis, Number of sickle cell crises, by Study and Treatment group.....	46
Table 12: FDA Exploratory Analysis: Patient Experiences on Study GLUSCC09-01, Number (%) of patients by study experience.....	47
Table 13: Exploring the impact of the Applicant’s imputation method on the distribution of sickle cell crisis events by treatment group	47
Table 14: Applicant Analyses: Number of sickle cell crises (SCC) by methods of imputation ...	49
Table 15: FDA Exploratory Analyses: Rates of sickle cell crisis counts per 48 weeks between treatment groups, Negative binomial regression	51
Table 16: Applicant sensitivity analyses of the primary efficacy endpoint using negative binomial regression, comparing rates of sickle cell crisis events per 48 weeks.....	51
Table 17: Secondary efficacy results, by Study and Treatment group	52
Table 18: Unplanned secondary efficacy endpoint: Incidence of Acute Chest Syndrome in Study GLUSCC09-01, by Treatment Group.....	53
Table 19: Unplanned secondary efficacy endpoint: Time to first sickle cell crisis, by Study and Treatment Group.....	54
Table 20: Unplanned secondary efficacy endpoint: Percentage of time hospitalized, by Study and Treatment Group.....	54
Table 21: Efficacy results among subgroups in Study GLUSCC09-01 by treatment group; rate of sickle cell crises per 48 weeks*	55
Table 22: Summary of Drug Exposure (Safety Population).....	59
Table 23: Demographics, Safety Population (Study 10478 and GLUSCC0901).....	60
Table 24: Summary of Mortality, by treatment group, (Safety Population)	62
Table 25: SAEs occurring in $\geq 2\%$ of Endari-treated Subjects, by SOC (Safety Population)	66
Table 26: SAEs occurring in $\geq 2\%$ of Endari-treated Subjects, by PT (Safety Population)	67
Table 27: Disposition of Subjects, Safety Population	69
Table 28: TEAEs leading to study drug withdrawal, Safety Population (N=298)	70
Table 29: TEAEs occurring in $\geq 10\%$ of Endari-treated Subjects, by PT (Safety Population).....	71
Table 30: Related TEAEs occurring in $\geq 1\%$ of Endari-treated Subjects, by PT (Safety Population).....	72
Table 31: Time Point Value and Change From Baseline in Hematology Parameters, Safety Population (N=298)	73

Clinical Review

NDA 208587

Endari® (L-glutamine)

Table 32: Changes in hematology parameters from baseline to end of treatment, Safety population	75
Table 33: Time Point Value and Change from Baseline in Serum Chemistry	75
Table 34: Summary of Serum Chemistry Parameters That Shifted to Low or High.....	76
Table 35: Laboratory results: Patient 0901-17-501	79
Table 36: Laboratory results: Patient 0901-14-502	80
Table 37: Laboratory results: Patient 0901-04-101	81
Table 38: Laboratory results: Patient 0901-09-514	82
Table 39: Subjects with TEAEs, by body weight, by treatment group (Safety Population)	84
Table 40: Subjects with SAEs, by body weight, by treatment group (Safety Population).....	84
Table 41: SAEs occurring in Endari treated subjects with baseline body weight <30kgs	84
Table 42: Number and percent of subjects with TEAEs by age group (5-12 years, 13-18 years and >18 years), Safety population	85
Table 43: TEAEs occurring in $\geq 10\%$ of Endari-treated subjects ≤ 18 years, (Safety Population).....	86
Table 44: TEAEs occurring in $\geq 5\%$ of Endari-treated subjects >18 years, (Safety Population)	86
Table 45: SAEs occurring in $\geq 2\%$ of Endari-treated Subjects, by age group (≤ 18 versus >18 years), Safety Population	87
Table 46: Subjects with SAEs by age group (5-12, 13-18 and >18 years), Safety population	88
Table 47: TEAEs occurring in $\geq 5\%$ of Endari treated subjects by PT, and by Sex (Safety Population).....	89
Table 48: AEs by HU use	92

Table of Figures

Figure 1: FDA Analysis: Distribution of sickle cell crisis events by treatment group, FDA sensitivity analysis population, N=20648
Figure 2: Distribution of sickle cell crises by treatment group under Applicant's imputation rule, ITT population, N=23048
Figure 3: FDA Analysis: Mean cumulative functions for sickle cell crisis events by treatment group50
Figure 4: FDA Analysis: Estimated 48-week sickle cell crisis event count by treatment group, recurrent event analysis, ITT population (N = 230)50
Figure 5: Study GLUSCC0901 Potential Hy's Law Plot – Total Bilirubin vs. ALT78

Table of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ACS	Acute chest syndrome
ANOVA	analysis of variance
BUN	Blood urea nitrogen
BP	Blood pressure
CI	Confidence interval
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case report form
FAS	Full analysis set
FDA	Food and Drug Administration
GGT	Gamma glutamyl transferase
Hb	Hemoglobin
HSCT	Hematopoietic stem cell transplantation
HU	hydroxyurea
HR	Hazard ratio
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
INR	international normalized ratio
ITT	intent-to-treat
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IV	Intravenous
Kg	Kilograms
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not available
NAD	Nicotinamide adenine dinucleotide
NADH	Reduced nicotinamide adenine dinucleotide
NDA	New Drug Application
Peds QL	Pediatric Quality of Life Questionnaires
PT	Preferred term
PK	Pharmacokinetics
PMC	Post-marketing commitment
PSUR	Periodic Safety Update Report
QOL	Quality of life
RBC	Red blood cells
RCT	Randomized control trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SBS	Short bowel syndrome
SCA	Sickle cell anemia

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

SCC	Sickle cell crises
SCD	Sickle cell disease
SD	Standard deviation
SOC	System organ class
SPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse events
ULN	Upper limit of normal
LLN	Lower limit of normal

1 Recommendations/Risk Benefit Assessment

1.1. Recommendation on Regulatory Action

This reviewer recommends regular approval of Endari for the indication of “the treatment of sickle cell disease”. Approval is based on the observed estimated mean cumulative rates of sickle cell crises of 3 versus 3.8 for Endari versus placebo treated patients respectively at Week 48 [Hazard ratio (HR) 0.73, 95% CI: (0.55, 0.99)]. This conclusion is supported by the comparable safety profile (serious adverse events (SAEs), SAEs related to study treatment, treatment emergent adverse events (TEAEs) and TEAEs that led to study drug withdrawal) of Endari in patients with sickle cell disease (SCD) compared to placebo; and the lower frequency of occurrence of disease related SAEs [sickle cell anemia with crisis and acute chest syndrome (ACS)] in patients with SCD treated with Endari versus placebo.

Based on the data in this submission, this reviewer agrees with the clinical pharmacology recommendation that a PMC should be issued to the Applicant to conduct an additional study post-approval to optimize the dose of Endari in patients with body weights of 65 kilograms or less.

1.2. Basis of the Recommendation

Table 1: Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Sickle-cell disease (SCD) is a life-threatening, chronic hemolytic anemia that affects nearly 100,000 individuals in the United States. Vaso-occlusive pain episodes /sickle cell crises (SCC) are the most frequent cause of recurrent morbidity in patients with SCD. The cumulative effect of recurrent vaso-occlusive episodes and chronic hemolytic anemia result in multiple end-organ complications and overall decreased life expectancy in patients with SCD. 	SCD is a serious and life threatening condition associated with reduced life expectancy.
Unmet Medical Need	<ul style="list-style-type: none"> Currently, management of SCC episodes is generally only supportive. Hematopoietic stem cell transplantation (HSCT) offers potential cure; however few patients are eligible for this treatment option. Hydroxyurea (HU) is the only approved drug for reducing the frequency of SCC in adult patients with SCD (1998). In some patients, HU use is complicated by severe, sometimes life-threatening, adverse effects (myelosuppression and malignancies). 	There is a huge unmet medical need for new drugs for the treatment of SCD.
Clinical Benefit	<ul style="list-style-type: none"> Study GLUSCC09-01 and Study 10478 were both multicenter, double-blind, randomized, placebo-controlled studies designed to evaluate the long-term efficacy and safety of Endari for the treatment of SCD in patients with sickle cell anemia and sickle β^0-thalassemia who were at least 5 years of age. The primary efficacy endpoint was the number of SCC at Week 48. For Study GLUSCC09-01: <ul style="list-style-type: none"> Per Applicants analysis, the median number of SCC at Week 48 was 3 versus (vs.) 4 for L-glutamine vs. placebo 	Endari treatment is associated with fewer sickle cell crises at Week 48 compared to placebo treatment.

Clinical Review
NDA 208587
Endari® (L-glutamine)

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	<p>treatment groups respectively (p=0.0052).</p> <ul style="list-style-type: none"> - Per FDA analysis, the estimated mean cumulative rates of SCC at Week 48 was 3 vs 3.8 for L-glutamine vs. placebo treatment groups [HR 0.73, 95% CI: (0.55, 0.99)] • For Study 10478: <ul style="list-style-type: none"> - The primary efficacy result was not statistically significant. - Study 10478 was excluded from FDA’s efficacy analysis due to imbalance in HU use at baseline and the high study discontinuation rate (57%). 	
Risks	<ul style="list-style-type: none"> • Three treatment emergent deaths occurred in L-glutamine treated subjects. None were considered treatment related. • The proportion of subjects with SAEs was similar between the L-glutamine (75.4%) and placebo treatment groups (80.2%). • The most common SAEs in the L-glutamine group were sickle cell anemia (SCA) with crisis (66.3%), ACS (7.0%), and pneumonia (4.8%). Majority of these SAEs were considered unrelated to Endari treatment by study investigators. • SCA with crisis and ACS occurred more frequently in the placebo group compared to the L-glutamine group (72% vs 66%) and (19 vs 7%) respectively. • TEAEs considered related to study drug occurred in 18.7% and 13.5% of Endari and placebo treated patients respectively. • The frequency of TEAEs was similar between treatment groups. Other than SCA with crisis, the most commonly reported TEAEs in Endari treated subjects were constipation, nausea, headache, pyrexia, abdominal pain, and cough. • Overall, there were no significant differences in safety by demographic variables between treatment groups. • No notable differences in changes in clinical chemistry or hematology parameters between treatment groups were observed. 	<p>In patients with SCD, the safety profile of Endari is comparable to that of placebo treatment.</p> <p>The most commonly reported adverse events in Endari treated subjects were constipation, nausea, headache, pyrexia, abdominal pain, and cough.</p> <p>The lower frequency of occurrence of SCA with crisis and ACS in Endari treated subjects suggests a beneficial treatment effect of Endari.</p>
Risk Management	<ul style="list-style-type: none"> • Studies 10478 and GLUSCC09-01 did not include subjects with hepatic or renal insufficiency. The safety of Endari in subjects with hepatic or renal insufficiency is not known. • In sub-group analysis of Study GLUSCC09-01, the median number of SCC at Week 48 in patients with baseline body weight of ≤ 65 kg treated with 10 or 20 grams per day of study drug was 2 vs. 2.5; relative risk: 0.87 (95% CI: 0.63, 1.19) for Endari vs. placebo treated patients respectively. 	<p>Labeling should reflect the absence of data on the long term safety of Endari in patients with renal or hepatic impairment.</p> <p>The dose of Endari in patients with body weight ≤ 65 kg may be sub-optimal.</p>

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

Analysis of Condition and Current Treatment Options

Sickle-cell disease (SCD) is a life-threatening, hereditary, chronic hemolytic anemia that affects nearly 100,000 individuals in the United States (Yawn, Buchanan et al. 2014). A single point mutation in the hemoglobin β -globin chain of affected persons produces mutant hemoglobin molecules (Hemoglobin S [Hb S]). The most common form of sickle-cell disease (homozygous Hb SS) accounts for 60%-75% of sickle cell disease in the United States. Approximately 25% of patients have coinheritance of Hb S with another β -globin chain variant such as sickle-Hb C disease and sickle β -thalassemia.

During periods of deoxygenation, Hb S polymerizes within erythrocytes resulting in intermittent vaso-occlusive events and chronic hemolytic anemia. Vaso-occlusion occurs as a result of the formation of multicellular aggregates that block blood flow in small blood vessels, resulting in tissue ischemia & reperfusion damage to downstream tissues which lead to recurrent acute pain/crises episodes. Vaso-occlusive pain episodes are the most frequent cause of recurrent morbidity in SCD and account for the majority of SCD-related hospitalizations (Platt, Thorington et al. 1991, Gill, Sleeper et al. 1995). The cumulative effect of recurrent vaso-occlusive episodes and sustained hemolytic anemia result in multiple end-organ complications including diastolic heart disease, pulmonary hypertension, splenic dysfunction; hepatobiliary disease and chronic kidney disease.

SCD is associated with decreased life expectancy (Platt 1994, Lanzkron, Carroll et al. 2013, Elmariah, Garrett et al. 2014, Maitra, Caughey et al. 2017). Acute chest syndrome (ACS) is a serious acute complication and a leading cause of mortality in both children and adults with SCD (Vichinsky, Neumayr et al. 2000, Bakanay, Dainer et al. 2005). Other causes of death in patients with SCD include infections (Adamkiewicz, Sarnaik et al. 2003) and cerebrovascular events (Platt 2005, Verduzco and Nathan 2009). Children have higher rates of death from infection and sequestration crises (Manci, Culberson et al. 2003). Cardiopulmonary complications represent a major mortality risk in adults (Fitzhugh, Lauder et al. 2010).

Currently, the management of sickle cell crises (SCC) episodes is generally supportive and includes symptomatic treatment with intravenous fluids, analgesics, oxygen and RBC transfusion support. Hematopoietic stem cell transplantation (HSCT) offers potential cure; however only few patients are eligible for this treatment option. Hydroxyurea (HU) is the only drug approved (1998) for reducing the frequency of sickle cell crises in adult patients with SCD. In a randomized, placebo-controlled study, HU decreased the frequency of painful crises, ACS, red blood cell (RBC) transfusion and hospitalization rates in adults with sickle cell anemia (Charache, Terrin et al. 1995)

Assessment of Efficacy

Studies 10478 and GLUSCC09-01 were both multicenter, double-blind, randomized, placebo-controlled studies designed to evaluate the long-term safety and efficacy of L-glutamine for the treatment of SCD in patients with sickle cell anemia and sickle β 0-thalassemia who were at least 5 years of age.

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

The primary efficacy endpoint was the number of SCC through Week 48 and prior to start of taper. This endpoint was considered reasonably likely to predict clinical benefit by the Division of Hematology Products.

In study GLUSCC09-01, a SCC was defined as a visit to an emergency room/medical facility for SCD-related pain that was treated with a parenterally administered narcotic or parenterally administered Toradol (ketorolac). The occurrence of chest syndrome (acute clinical pulmonary findings corroborated by findings of a new pulmonary infiltrate on chest X-ray films), priapism, and splenic sequestration were considered SCC even if the symptoms were not painful enough to require narcotics or Toradol (ketorolac). Splenic sequestration was defined as an increase in spleen size associated with pain in the area of the organ along with a decrease in the hemoglobin concentration of at least 2 g/dL within a 24-hour period. Determination of whether any given crisis episode met the criteria for the primary end point was adjudicated by a Central Adjudication Committee (CAC).

In study 10478, SCC was defined as a visit to a medical facility that lasted more than 4 hours (from the date/time of registration to the date/time of departure) for an acute sickling-related pain; treated with a parenterally administered narcotic (except for facilities in which only orally administered narcotics were used). The occurrence of chest syndrome (chest-wall pain in association with findings of a new pulmonary infiltrate on chest x-ray films and fever), priapism, and hepatic or splenic sequestration (a sudden increase in liver or spleen size associated with pain in the area of the organ, a decrease in the hemoglobin concentration of at least 2 grams per deciliter (g/dL), and, for liver sequestration, abnormal change in liver function tests not due to biliary tract disease) was to be considered a crisis; the occurrence of hematuria and exacerbations of pain was not considered a crisis. The primary endpoint was not adjudicated by a CAC in Study 10478.

Efficacy results from Studies 10478 and GLUSCC09-01 were not considered comparable, due to differences in the definitions and classification of the primary endpoint; the lack of stratification of randomization by HU in Study 10478, the wider range of crises within the 48-week treatment period in Study 10478 compared to Study GLUSCC09-01 and the high and differential early study dropout rates between treatment arms in both studies.

Efficacy was demonstrated by a reduction in the number of SCC through Week 48 and prior to the start of tapering among patients who received Endari compared to patients who received placebo. Per the Applicants' analysis, the median number of SCC at Week 48 was 3 vs 4 for the L-glutamine vs. placebo groups respectively (p=0.0052). FDA analysis estimated mean cumulative rates of SCC of 3 vs 3.8 for Endari vs placebo treatment groups at 48 weeks [Hazard ratio 0.73, 95% CI: (0.55, 0.99)]. Treatment with Endari also resulted in fewer median number of hospitalizations for sickle cell pain: 2 vs 3 for Endari vs placebo group (p=0.0045), fewer cumulative days in hospital: 6.5 vs 11 days in the Endari vs placebo group (p=0.022) and lower incidence of ACS in the Endari vs placebo group (0.0028) across the 48-week treatment period. Study 10478 failed to meet its specified significance level for both primary and secondary efficacy analyses, although this study also showed a trend in favor of L-glutamine over placebo (Median number of SCC at Week 48 was 4 vs 5 for the Endari vs. placebo groups respectively (p=0.072).

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

The statistical analysis of the efficacy results was complicated by a high and differential rate of patient discontinuation from the study before completion of the full 48-week treatment period, which necessitated invocation of imputation methods all of which had important limitations due to required assumptions for the methods. In sensitivity analyses conducted by FDA, the reduction in crises over 48 weeks from L-glutamine treatment compared to placebo ranged from 0.4 to 0.9 crises. Together, these exploratory analyses can be interpreted as showing a modest trend supporting a claim of benefit for Endari.

Assessment of Safety

The safety population consisted of 298 subjects (enrolled in studies GLUSCC09-01 and 10478), who received at least 1 dose of study medication, excluding patients from one site in Study 10478 (Site 106) excluded from the analysis due to potential scientific misconduct by the investigator at this site. Data from 5 smaller studies (Studies 8288, 8822, 8775, 10779, and 10511) conducted early in the clinical development program of L-glutamine were not included in the integrated analyses because safety data in these studies were not as explicitly defined or collected as in Study 10478 and Study GLUSCC09-01 (Study 8822 was a dose-finding study and did not collect AE data).

The majority of subjects in the safety population were black or African American (97.3% in the L-glutamine treatment group and 96.4% in the placebo treatment group). Fifty-seven percent were adults (> 18 years of age). Ninety percent of subjects in the overall safety population had a diagnosis of sickle cell anemia (SCA) and 63.4% were being treated with HU at baseline (66.3% in the L-glutamine treatment group and 58.6% in the placebo treatment group). In Study 10478, the mean number of SCCs in the year prior to screening was 9.8 and 8.8 in the L-glutamine and placebo treatment groups, respectively. In Study GLUSCC09-01, the mean number of SCCs in the year prior to screening was 3.9 and 4.1 in the L-glutamine and placebo treatment groups, respectively. The safety results are summarized below:

- Overall, 72 subjects (38.5%) in the L-glutamine treatment group and 40 subjects (36.0%) in the placebo treatment group discontinued the study before Week 48. Reasons for discontinuation of treatment were similar between treatment groups: the most common reason for discontinuation in both treatment groups was consent withdrawn (26 subjects [13.9%] in the L-glutamine treatment group and 14 subjects [12.6%] in the placebo treatment group). FDA's review of the narratives of subjects who withdrew consent revealed a variety of reasons which did not appear related to study treatment.
- Four deaths occurred in safety population. All 4 deaths occurred in Endari-treated subjects. Three deaths were treatment emergent. The 4th death occurred 130 days after last treatment with Endari. None of the 3 treatment emergent deaths were considered related to Endari treatment by the investigators. In the absence of autopsy findings, FDA is unable to comment on the relatedness of these events to Endari treatment.
- At least one treatment-emergent SAE occurred in 141 subjects (75.4%) in the L-glutamine treatment group and 89 subjects (80.2%) in the placebo treatment group. The most common SAEs occurring in the Endari group were SCA with crisis (66.3%), ACS

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

(7.0%), and pneumonia (4.8%). Majority of these SAEs were considered unrelated to L-Glutamine treatment by the Applicant. In the L-glutamine group, SAEs considered by the investigator to be related to study drug included hypersplenism (n=1), sickle cell anemia with crisis (n=1), abdominal pain (n=1), and chest pain (n=1).

- Other than sickle cell anemia with crisis which occurred in majority of L-glutamine and placebo treated patients, the most commonly reported TEAEs were constipation (21.4% L-glutamine and 18.0% placebo), nausea (19.3% L-glutamine and 14.4% placebo), headache (18.2% L-glutamine and 15.3% placebo), pyrexia (17.1% L-glutamine and 27.9% placebo), and cough (15.5% L-glutamine and 13.5% placebo).
- TEAEs were considered related to study drug by investigators in 18.7% versus 13.5% of subjects in the Endari and placebo treatment groups respectively. Treatment-emergent AEs leading to study drug discontinuation occurred in 5 subjects (2.7%) in the Endari treatment group and 1 subject (0.9%) in the placebo treatment group.

Literature review:

The Applicant reported that:

- From August 1 2008 to June 10, 2011: 6 studies were identified in which subjects were exposed to L-glutamine. These studies did not include case reports of any individuals who experienced AEs related to L-glutamine administration.
- From June 11 2011 to June 10 2015: 39 studies were identified in which subjects were exposed to L-glutamine however none of the glutamine used in any of the studies was NutreStore. These studies did not include any reports of individuals who experienced AEs related to L-glutamine administration.
- From June 11 2015 to June 10 2016: 6 studies were identified in which subjects were exposed to L-glutamine. None of the glutamine used in these studies was NutreStore. One paper did not identify the source of the glutamine used. None of the studies reported AEs that were attributable to L-glutamine supplementation.

A search of the Medline (PubMed) database by FDA revealed 17 eligible publications that permitted an evaluation of the safety of L-glutamine or glutamine in humans. These included some studies that used multiple active ingredients in addition to glutamine. Overall, a relatively substantial level of safety of L-glutamine was found. In all studies reviewed, L-glutamine was relatively well tolerated with no significant increase in toxicity.

Overall Benefit-Risk Assessment:

SCD is a serious and life-threatening condition associated with recurrent vaso-occlusive pain or crises episodes and chronic hemolytic anemia. The cumulative effect of recurrent vaso-occlusive episodes and sustained hemolytic anemia result in multiple end-organ complications and a decreased life expectancy. Hydroxyurea is the only drug approved for reducing the frequency of sickle cell crises in adult patients with SCD. There is a huge unmet medical need for new drugs for the treatment of SCD.

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

In a multicenter, randomized, double-blind, placebo- controlled study (Study GLUSCC09-01), patients with sickle cell anemia and sickle β^0 -thalassemia (≥ 5 years of age) who had 2 or more painful crises in the 12 months prior to enrollment were treated with Endari or placebo and evaluated for efficacy and safety through Week 48. FDA analysis estimated the mean cumulative rates of SCC of 3 vs 3.8, for L-glutamine vs placebo group at 48 weeks [HR 0.73, 95% CI: (0.55, 0.99)]. Per the Applicants analysis, the median number of SCC at Week 48 was 3 vs 4 for the Endari vs. placebo groups respectively ($p=0.0052$). Treatment with Endari also resulted in fewer hospitalizations due to sickle cell pain at Week 48, cumulative days in hospital and a lower incidence of acute chest syndrome across the 48-week treatment period.

The statistical analysis was complicated by a high and differential rate of patient discontinuation from the study before completion of the full 48-week treatment period, which necessitated invocation of imputation methods. FDA sensitivity and exploratory analyses showed a trend in favor of L-glutamine.

The safety review revealed no significant safety concerns overall. Three treatment emergent deaths occurred in L-glutamine-treated subjects. None of these deaths were considered related to L-glutamine treatment by Investigators. The proportion of subjects with SAEs, TEAEs, drug related SAEs, drug related TEAEs and TEAEs that lead to study withdrawal was comparable between the treatment groups. The lower frequency of SCA with crisis and lower frequency of acute chest syndrome in Endari treated subjects suggest a beneficial effect. As expected for this population, the most common adverse event in study subjects was SCA with crises. Other common adverse events in L-glutamine treated subjects were: constipation (21.4%), nausea (19.3%), headache (18.2%), pyrexia (17.1%) and cough (15.5%).

Although some caution is warranted in interpretation of the primary efficacy results from Study GLUSCC09-01, in both the Applicants' and FDA's analysis, Endari treatment was associated with fewer sickle cell crises at Week 48 compared to placebo treatment. This finding is supported by the observed fewer hospitalizations due to sickle cell pain, cumulative days in hospital and a lower incidence of ACS in Endari treated patients across the 48-week treatment period. The lower frequency of disease related SAEs (SCA with crisis and ACS) in Endari treated subjects provides further support for a beneficial effect of Endari treatment in patients with SCD. Considering the observed favorable safety profile of Endari in safety population, the potential benefit from treatment with Endari appears to outweigh the risks in patients with SCD.

1.3 Recommendations for Labeling

The following key recommendations for the Endari Prescribing Information are based on this review:

- Revise the indication statement to provide the goals of therapy and clearly identify the patient population for whom treatment with Endari is indicated.
- Revise section 6.1 of the label to include demographics of the safety population and specify the number of subjects enrolled in the phase 2 and phase 3 studies.
- Include a description of serious adverse events and deaths that occurred in patients treated with L-glutamine in the text of Section 6.1.

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

- Include all adverse reactions that occurred in L-glutamine treated subjects in the label regardless of causality
- Combine all abdominal pain preferred terms in a grouped term analysis and define the terms that are grouped as a footnote to the table describing adverse events in Section 6.1.
- Include the safety results from pediatric subjects studied in Study 10478 and Study GLUSCC0901 in Section 8.4.
- Include the definition of the primary endpoint- sickle cell crises in Section 14.

1.4 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

None

1.5 Recommendations for Post-market Requirements and Commitments

The proposed total daily dose of Endari is 10 grams, 20 grams, or 30 grams orally, in two divided doses based on body weight. In the Applicant's single dose finding study (Study 8288); L-glutamine doses of 10 grams per day and 20 grams per day did not increase the ratio of NADH to total NAD levels from the baseline in adult patients with SCD.

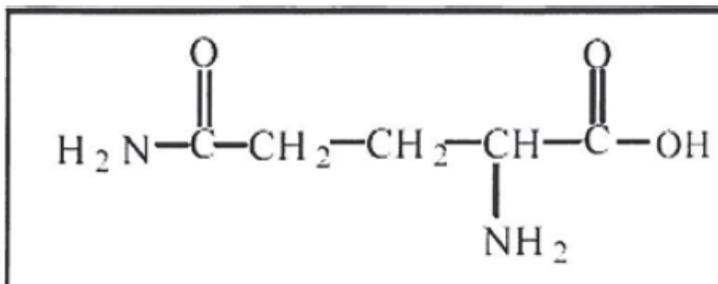
In Study GLUSCC09-01, subgroup efficacy analysis suggested a lower benefit of Endari in patients with baseline body weight of ≤ 65 kg treated with 10 grams per day or 20 grams per day of L-glutamine compared to placebo [Endari 2 vs. placebo 2.5 crises in 48 weeks; relative risk: 0.87 (95% CI: 0.63, 1.19)]. In subjects who received a total daily dose of Endari of 30grams, the relative risk was 0.56 [95% CI: 0.41, 0.77] in favor of Endari.

This reviewer agrees with the FDA Clinical Pharmacology reviewer's recommendation for the conduct of a 24-week clinical trial in adult and pediatric patients with SCD to identify an effective dose of Endari in patients with body weight ≤ 65 kg that increases the ratio of NADH to total NAD levels from the baseline as compared to a dose of 30 grams per day in patients with body weight > 65 kg. This study should also be designed to demonstrate comparative efficacy and safety of Endari at the effective dose in patients with body weight ≤ 65 kg. The study population should reflect the typical population of patients with SCD in the United States, and should include patients with renal and hepatic impairment.

2 Introduction and Regulatory Background

2.1. Product Information

Drug Established Name: L-glutamine
Proposed Trade Name: Endari
Dosage Forms: Oral Powder: 5 g of L-glutamine powder per paper-foil-plastic laminate packet
Pharmacologic Class: Amino acid
Chemical Structure:



Mechanism of Action: The mechanism of action of L-glutamine in SCD is not fully understood. L-glutamine may increase the activity of NAD synthesis and improve NAD redox potential in sickle RBCs to counter the oxidant-dependent pathophysiology of the disease.

Proposed Indication: For the treatment of sickle cell disease (SCD)

Proposed Dose-Schedule: 0.3g/kg body, maximum dose 30g/day

Administer orally, twice per day, based on body weight according to the following schedule:

Weight (kilograms)	Weight (pounds)	Per dose in grams	Per day in grams
less than 30	less than 66	5	10
30 - 65	66 - 143	10	20
greater than 65	greater than 143	15	30

Other Indications:

In the US, NutreStore® (L-glutamine powder for oral solution) is currently indicated for:

Clinical Review

NDA 208587

Endari® (L-glutamine)

- The treatment of short bowel syndrome (SBS) in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone that is approved for this indication.

(b) (4)

2.2. Currently Available Treatments for Proposed Indication

Droxia (Hydroxyurea capsules, USP) is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally, at least 3 during the preceding 12 months).

2.3. Availability of Proposed Active Ingredient in the United States

There is currently one approved L-glutamine product in the US (NDA 21667, 06/10/2004) - NutreStore® (L-glutamine powder for oral solution). The composition of the drug product and the manufacturing process for Endari (L-glutamine oral powder) to be marketed for the treatment of SCD are the same as those used in the NutreStore product. See CMC review for additional information.

2.4. Important Issues with Consideration to Related Drugs

L-glutamine is a conditionally essential amino acid (molecular formula: C₅H₁₀N₂O₃; molecular weight: 146.15) found in the body. Endogenous L-glutamine plays a major role in various metabolic activities, including the formation of glutamate and the synthesis of proteins, nucleotides and nucleic acids. L-glutamine is eliminated by glomerular filtration, but it is reabsorbed by the renal tubules. Exogenous L-glutamine is anticipated to undergo similar metabolism.

There are no known safety concerns associated with the use of NutreStore®, L-glutamine powder for oral solution. L-glutamine is also available over-the-counter as a dietary/nutritional supplement. Overall, the reviewed scientific literature demonstrates a substantial level of safety with supplemental L-glutamine or glutamine.

2.5. Summary of Pre-submission Regulatory Activity Related to Submission

Date	Discussion
May 15, 1997	IND originally filed by Yutaka Niihara, MD, MPH
August 1, 2001	L-glutamine granted orphan drug designation by the FDA Office of Orphan Products Development
November 19, 2001	End of Phase 2 meeting held to gain understanding of the processes/requirements, guidance's, data management, labeling

Clinical Review

NDA 208587

Endari® (L-glutamine)

	requirements, and good manufacturing practices for the submission of a NDA for L-glutamine for the treatment of sickle cell disease.
January 7, 2005	Granted Fast-Track designation
July 10, 2006	Correspondence from the FDA in response to information provided by Emmaus to FDA provided Clinical and pharmacology/toxicology comments and recommendations to the Sponsor regarding Protocol 10478
April 20, 2009	End of Phase 2 meeting held to discuss the design of the Phase 3 study.
January 6, 2010	FDA provided advice to the applicant regarding the clinical and statistical design of the Phase 3 study.
August 2, 2011	IND was transferred to the current sponsor, Emmaus Medical Inc.
November 5, 2012	Type C Meeting held to obtain feedback on the Interim Analysis Report of the Phase 3 study.
June 11, 2014	Type C Meeting held to obtain the Division's feedback on the proposed NDA plan. Preliminary findings from the Phase 3 trial were presented and discussed.
October 15, 2014	Type A Meeting held to discuss the analysis of the completed Phase 3 study (Study GLUSCC09-01).

2.6. Other Relevant Background Information

On June 10, 2004, L-glutamine was approved under NDA 21,667 and marketed as NutreStore (L-glutamine powder for oral solution) for the treatment of SBS in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone approved for this indication.

In September 2006, an application (NDA

(b) (4)

2.7. Compliance with the Pediatric Research Equity Act

Since L-glutamine has orphan designation for the treatment of SCD, this submission is exempt from the requirements of the Pediatric Research Equity Act.

Clinical Review

NDA 208587

Endari® (L-glutamine)

3 Ethics and Good Clinical Practices

3.1. Submission Quality and Integrity

This NDA was submitted on September 7, 2016 in eCTD format. FDA had no concerns regarding the submission quality of the data submitted. The applicant requested priority review. The application was filed on November 6, 2016. Standard review was granted. Additional amendments post filing are listed in the table below.

Table 2: NDA Submission and Amendments

eCTD SN	Received	Category	Subcategory
0026	05/19/2017	Clinical	Response To Information Request
0025	05/18/2017	Clinical	Response To Information Request
0024	05/17/2017	Biometrics; Patent & Exclusivity/Patent Information	Response To Information Request
0023	05/23/2017	Clinical	Response To Information Request
0022	05/05/2017	Quality	Response To Information Request
0021	05/05/2017	Clinical	Response To Information Request
0020	05/05/2017	Clinical	Response To Information Request
0019	03/24/2017	Waiver Request	Other
0018	03/17/2017	Amendment Correspondence	Amendment Verification Statement
0017	03/17/2017	Clinical	Response To Information Request
0016	03/16/2017	Clinical	Response To Information Request
0015	03/02/2017	Labeling	Container-Carton Draft
0014	02/24/2017	Labeling	Container-Carton Draft
0013	02/10/2017	Clinical	Response To Information Request
0012	02/01/2017	Clinical	Response To Information Request
0011	01/23/2017	Biometrics	Response To Information Request
0010	01/13/2017	Clinical	Response To Information Request
0009	01/11/2017	Clinical; Clinical Pharmacology	Clinical Information; Response To Information Request
0008	01/09/2017	Clinical	Safety Update
0007	12/16/2016	Biometrics	Response To Information Request
0006	12/09/2016	Labeling; Clinical	Package Insert Draft; Response To Information Request
0005	12/02/2016	Clinical	Response To Information Request
0004	12/01/2016	Biometrics	Response To Information Request
0003	11/30/2016	Proprietary Name	Request for Review
0002	11/18/2016	Non-Clinical	Response To Information Request
0001	10/18/2016	Quality	Response To Information Request

Clinical Review

NDA 208587

Endari® (L-glutamine)

3.2. Compliance with Good Clinical Practices

This application is primarily supported by data from Study GLUSCC0901 and Study 10478.

The pivotal study supporting this application was Study GLUSCC09-01 - “A Phase III, prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter study of l-glutamine therapy for sickle cell Anemia and Sickle β^0 -Thalassemia”. Per the Applicant, this study was conducted in full compliance with the principles of the "Declaration of Helsinki", International Conference on Harmonization (ICH) guidelines, and all of the applicable US Code of Federal Regulations (CFR), 21 CFR Part 50 and 312.

Study 104788 was “A phase II, prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter study of L-glutamine therapy for sickle cell anemia and sickle β^0 -thalassemia”. Per the Applicant, with the possible exception of one site (Site 106), the study was performed in accordance with the U.S. Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, as well as the clinical research guidelines established by the basic principles defined in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP, 1996). During study monitoring visits, potential investigator misconduct and suspected fraud were reported at Site 106. Due to the research noncompliance at this site, results from 11 patients enrolled at this site were excluded from the primary efficacy and safety analyses.

In Studies 10478 and GLUSCC09-01, before any study-related procedures were performed, informed consent and/or assent was obtained from each patient or the patient’s legally authorized representative using appropriate IRB approved informed consent and/or assent forms.

Office of Scientific Investigations (OSI) Inspection

Three study sites for GLUSCC09-01 (Sites 02, 14 and 21) and one site (Site 101) for Study 10478 were selected for audit and inspection by OSI. These sites were selected based on the enrollment numbers and the potential impact of results from these sites on the overall study results. At all sites inspected, source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study efficacy endpoints of sickle cell crisis and acute chest syndrome. Subject disposition was verified.

At all 4 clinical sites, study efficacy endpoint(s) were verifiable and no under-reporting of adverse events or serious adverse events were noted.

Study 10478

OSI inspection at Site 101 was conducted from February 6 to 13, 2017. At this site, 42 subjects were screened, 25 subjects were randomized, and 12 subjects completed the study. The reasons for discontinuations from the study in the 13 subjects included non-compliance with study drug (3), lost to follow-up (2), not meeting inclusion criteria (2), consent withdrawal (2), death (1), lack of efficacy (1), missed 4 visits (1), and commitment illness (1).

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

A Form FDA 483 was issued to the site for failure to conduct an investigation in accordance with investigational plan. The identified deficiencies were:

- Violations of inclusion criteria: Seven subjects who had < 2 painful crises in the previous 12 months were enrolled in the study. The PI (previous sponsor for this investigator-initiated study) granted waiver for the enrollment.
- Deviations of exclusion criteria: Nineteen of the 25 enrolled subjects had no INR tests to assess exclusion criterion of INR > 2.0 (10 subjects in L-glutamine group and 9 subjects in placebo group), one subject had serum albumin < 3.0 g/dL (in the L-glutamine group), and one subject received blood product within 3 months prior to enrollment (in placebo group).

The principal investigator at this site adequately responded to the inspection findings in a letter dated March 6, 2017.

Although some regulatory violations were noted, this reviewer agrees with OSI's conclusion that this is unlikely to significantly impact the integrity of data collected and the data generated by this site may be used in support of the respective indication.

Study GLUSS09-01

OSI inspection at Site 02 was conducted from January 5 to 18, 2017. At this site, 32 subjects were screened, 23 subjects were randomized, and 12 subjects completed the study. The reasons for discontinuations from the study in the 11 subjects included consent withdrawal (2); non-compliance with study drug (2); relocation (2); death (2); lost to follow-up (1); wrong type of thalassemia at enrollment (1); and pregnancy (1).

A Form FDA 483 was issued to the site for failure to conduct an investigation in accordance with investigational plan and failure to prepare accurate case histories with respect to observations and data pertinent to the investigation. The specific identified deficiencies were:

- Violations of inclusion criteria: Two subjects were initially checked as eligible subjects but late corrected as not eligible subjects.
 - One subject (#101, placebo group) initially met the inclusion criteria requirement of having 2 painful crises within 12 months of enrollment; however this subject received a transfusion within 3 months of screening and thus could not be enrolled at the time. The subject was enrolled in the study later without further verification for requirement of 2 painful crises within 12 months. The subject discontinued from the study subsequently after identification.
 - One subject (#102, L-glutamine group) had sickle β^+ Thalassemia as per the hemoglobin electrophoresis results and not sickle β^0 Thalassemia as required in the study eligibility criteria. The investigator reported this violation to the study sponsor and IRB. The subject discontinued from the study thereafter.
- One subject (#503, L-glutamine group) not currently using hydroxyurea (HU) treatment was incorrectly stratified for randomization with the hydroxyurea user group.

Clinical Review

NDA 208587

Endari® (L-glutamine)

- One subject (#104, L-glutamine group) was dispensed the incorrect amount of study medication based on body weight, 20 gram instead of 30 gram per day at visit 2. The dosage was corrected on visit 3/Week 4.
- Several minor missing and inaccurate recording of commitment medications and action taken for adverse events were noted.

The principal investigator at this site adequately responded to the inspection findings in a letter dated February 8, 2017.

Although some regulatory violations were noted, this reviewer agrees with OSI's conclusion that this is unlikely to significantly impact overall data integrity and the data generated by this site may be used in support of the respective indication.

3.3. Financial Disclosures

The applicant provided certification on FDA Form 3454 to indicate that there were no financial arrangements between the Sponsor and Investigators which could be affected by the outcome of study 10478 and GLUSCC09-01. The Clinical Investigators had no proprietary interest in the product, no significant equity in the sponsor and no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(1). However, the Chairman and CEO of Emmaus Inc., the Applicant, was the Principal Investigator at one of the study sites for Study 10478.

4 Significant Issues Related to Other Review Disciplines

4.1. Chemistry Manufacturing and Controls

At the time of completion of this review, the Chemistry Manufacturing and Controls review was pending.

4.2. Preclinical Pharmacology/Toxicology

The following is a summary of relevant information taken from the Pharmacology/Toxicology Review and Evaluation by Dr. Shwu-Luan Lee dated June 1, 2017:

The nonclinical information in this application is derived entirely from pharmacodynamic, pharmacokinetic (PK), and toxicology data in the scientific literature and additional toxicology studies provided by the L-glutamine supplier (b) (4)

Other pharmacology/toxicology data used to support this 505(b)(2) NDA were previously reviewed under NDA 21667.

The rationale for using L-glutamine in the treatment of SCD is derived from published scientific articles. Increases in the rate of glutamine transport and higher active red cell glutamine affinity may increase glutamine availability, and increase the total NAD content in sickle red blood cells. Research data suggests that sickle RBCs have decreased NAD redox potential, manifested as decreased NADH/[NAD+ plus NADH] ratios, when compared with normal RBCs. Sickle RBCs

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

also have higher total NAD content than normal RBCs. The decreased NAD redox potential renders sickle RBCs more susceptible to oxidative damage. Oxidative damage may result in stimulation of inflammatory processes and expression of adhesion molecules in RBCs. Thus L-glutamine may improve the condition of sickle RBCs by increasing the NAD redox potential and NADH levels, thereby preventing some of the oxidative damage they typically experience.

Most of the safety toxicology studies for L-glutamine for this application were reviewed under NDA 21667. In summary, the oral LD50 values were approximately 20 g/kg in mice and rabbits and approximately 10 g/kg in rats. The potential targets of organs of toxicity include the stomach, liver, and kidney.

Dr. Shwu-Luan Lee concluded that L-glutamine is approvable for the proposed indication from the perspective of Pharmacology/Toxicology.

4.3. Clinical Pharmacology

4.3.1 Mechanism of Action

L-glutamine is an amino acid found in the body. It is the preferred fuel for rapidly dividing cells including hematopoietic cells and serves as a precursor of nucleic acids and nucleotides including the pyridine nucleotides - NAD and NADH. Studies suggest that sickle RBCs have high NAD levels and decreased NAD redox potential, when compared to non-sickle RBCs. Sickle RBCs may respond to oxidant stress by producing more NAD, but that this response may be overwhelmed resulting in an overall decrease in redox potential (Zerez, Lachant et al. 1988). The decreased NAD redox potential renders sickle RBCs more susceptible to oxidative damage. Studies have shown that oxidative phenomena may play a significant role in the pathophysiology of SCD and that increased susceptibility to oxidation of sickle RBCs may contribute to chronic hemolysis (Bensinger and Gillette 1974) and vaso-occlusive events in SCD (Hebbel, Boogaerts et al. 1980).

In sickle RBCs, there is a higher affinity for and enhanced transport of L-glutamine and enhanced conversion of actively transported L-glutamine to glutamate (a byproduct of L-glutamine in NAD synthesis) compared to controls (Nihara, Zerez et al. 1997). Increases in the rate of glutamine transport and higher active red cell glutamine affinity may increase glutamine availability, and increase the total NAD content in sickle red blood cells.

The mechanism of action of L-glutamine in SCD is not fully understood. L-glutamine supplementation may increase the NAD redox potential and NADH levels in sickle RBCs, thereby preventing of the oxidative damage.

4.3.2 Pharmacokinetics

The following is a summary of relevant information taken from the Clinical Pharmacology Review by Dr. Yuhong Chen and Dr. Stacy Shord dated 5/31/2017.

Absorption: Following a single oral dose of 0.1 g/kg (~8.5 g), mean peak L-glutamine concentration of 1028 μ M (150 μ g/mL) occurred approximately 30 minutes after administration.

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

Enteral glutamine administration increased plasma glutamine levels in a dose-dependent manner to levels as high as 2773 $\mu\text{mol/L}$ following administration of 126 mmol/hr of enteral glutamine. An oral glutamine dose of 0.3 g/kg (equivalent of 18 g to 32 g) resulted in a peak plasma concentration of $1328 \pm 99 \mu\text{mol/L}$ at 45 minutes after dosing.

The PK following multiple oral doses has not been characterized. The effect of food on L-glutamine has not been evaluated.

Distribution: After an intravenous bolus, the volume of distribution is estimated to be $\sim 200 \text{ mL/kg}$.

Elimination: After an intravenous bolus, the terminal half-life is ~ 1 hour.

Endogenous L-glutamine participates in various metabolic activities, including the formation of glutamate and the synthesis of proteins, nucleotides, and amino sugars. Exogenous L-glutamine is anticipated to undergo similar metabolism.

L-glutamine is eliminated by glomerular filtration, but it is reabsorbed by the renal tubules.

Drug Interactions: No drug interaction studies have been conducted.

Specific Populations: The PK of L-glutamine was evaluated in 13 patients 3 years to 18 years of age with a hematologic or solid tumor malignancy. A single oral (or nasogastric tube in 2 patients) dose was administered as follows: 0.35 g/kg to 3 patients, 0.5 g/kg in 6 patients, 0.65 g/kg in 3 patients. The mean time to the maximum concentration (T_{max}) ranged from 40 minutes to 80 minutes and the mean area under the curve (AUC) increased in a less than dose-proportional manner.

The effect of body weight, organ impairment or other intrinsic factors on the PK or PD has not been evaluated.

Evidence submitted: Emmaus relied on publicly available data from published literature and the NutreStore labeling to describe the clinical pharmacology of Endari. No dedicated clinical pharmacology studies were conducted. In the pivotal phase III trial (GLUSCC09-01) and the supportive phase II trial (Study 10478), PK or PD samples were not collected. The dosing regimen administered in these trials was based on a single dose finding trial (Study 8288). The dose selection in Study 8288 was based on the changes in the ratio of NADH to total NAD levels from baseline in 11 adults with sickle cell disease. The proposed total daily dose of Endari is 10 grams, 20 grams, or 30 grams divided into two doses; is based on body weight.

Review: The key review issue for clinical pharmacology was focused on the appropriateness of the recommended dose of Endari in patients with body weight ≤ 65 kg. The available data suggest that L-glutamine does not provide similar benefit in patients weighing ≤ 65 kg compared to patients weighing > 65 kg.

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

In Study GLUSCC09-01, patients weighing ≤ 65 kg received a total daily dose of 10 grams or 20 grams of Endari. For the primary efficacy analysis, Endari was associated with reduced median frequency of SCC at Week 48 compared to placebo [Endari 3 vs. placebo 3.8 crises; relative risk: 0.73: 0.73 (95% CI: 0.55, 0.99)]. However, subgroup analysis suggested that patients with body weight ≤ 65 kg treated with Endari at dose levels 10 grams per day or 20 grams per day may not have as much benefit from L-glutamine treatment compared to placebo [L-glutamine 2 vs. placebo 2.5 crises in 48 weeks; relative risk: 0.87 (95% CI: 0.63, 1.19)]. Furthermore, in the single dose finding study (Study 8288), these dose levels (10 grams or 20 grams) of L-glutamine did not increase the ratio of NADH to total NAD levels from the baseline in adult patients with SCD.

Recommendations: The Application was recommended for approval by the Office of Clinical Pharmacology based on the totality of evidence. A post-marketing commitment (PMC) was issued to recommend that the Applicant conduct a 24-week clinical trial in adult and pediatric patients to identify a dose in patients with body weight ≤ 65 kg that similarly increases the ratio of NADH to total NAD levels from the baseline as compared to a dose of 30 grams per day in patients with body weight > 65 kg, and that demonstrates comparative efficacy and safety to a dose of 30 grams per day in patients with body weight > 65 kg.

4.4. Interdisciplinary Review Team (IRT)

Not Applicable

4.5. Pharmacovigilance

At the time of completion of this review, the final assessment from the Division of Pharmacovigilance was pending.

5 Sources of Clinical Data

5.1. Tables of Clinical Studies as listed by the Applicant in Module 5.2

Table 3: Table Clinical Trials

Study	Title	Population	Study Design
GLUSCC 09-01	A Phase 3, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study	Patients with Sickle Cell Anemia and Sickle β^0 -Thalassemia	Randomized, Double-blind, placebo-controlled, parallel-group
10478	A Phase 2, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study	Patients with Sickle Cell Anemia and Sickle β^0 -Thalassemia	Randomized, double-blind, placebo-controlled, parallel-group
8775	Prospective Randomized Crossover Double-Blind Trial	Patients with Sickle cell anemia	Double-blind, placebo-controlled, crossover
8822	A Dose-Finding Study of L-glutamine in Patients With Sickle Cell	Patients with Sickle cell anemia	Dose-finding study
10511	The Effect of L-Glutamine on Exercise Tolerance in Sickle Cell Patients	Patients with sickle cell anemia or sickle β^0 -thalassemia	Exercise tolerance study
10779	L-glutamine Therapy Increases Exercise Endurance of Sickle Cell	Subjects with sickle cell anemia or control	Exercise study
8288	Oral L-Glutamine Therapy for Sickle Cell Anemia	Subjects with sickle cell anemia	Pilot study

FDA generated table

5.2. Review Strategy

This review is based on information and analysis in this NDA submission. The key studies/materials used for the review of efficacy and safety for the sought indication were:

- Study GLUSCC09-01 (pivotal Phase 3 study).
- Study 10478 (Phase 2 study)
- LEGACY Studies: Study 8288, 8775, 10779, 10511
- Safety information for oral L-glutamine from the published literature
- The Periodic Safety Update Report for L-glutamine

The details of the protocol design for Study 10478 and Study GLUSCC09-01 are described in Section 6. Relevant results from the review of the protocols included in this submission are described in Section 5.3.

The Applicant's safety analyses were replicated for confirmation and supplemented where necessary by the FDA. Statistical analyses by the clinical reviewer were performed using (b) (4), and MedDRA Adverse Events Diagnostic (MAED) v1.2 (b) (4).

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

5.3. Discussion of Individual Studies/Clinical Trials

5.3.1. Study GLUSCC09-01:

A Phase III, Prospective, Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multicenter Study of L-Glutamine Therapy for Sickle Cell Anemia and Sickle β^0 -Thalassemia

GLUSCC09-01 was the pivotal study supporting this NDA. This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the long-term safety and efficacy of L-glutamine for the treatment of SCD in adult and pediatric subjects patients with sickle cell anemia and sickle β^0 -thalassemia.

The primary objective was to determine the efficacy of oral L-glutamine as a therapy for sickle cell anemia and sickle β^0 -thalassemia as evaluated by the number of occurrences of sickle cell crises. The secondary efficacy objectives were to assess the effect of oral L-glutamine on the frequency of hospitalizations for sickle cell pain; frequency of emergency room/medical facility visits for sickle cell pain; and hematological parameters (hemoglobin, hematocrit, and reticulocyte count).

Study Population

The study population consisted of 230 patients with SCD who were at least 5 years and older and who had had at least 2 episodes of painful crises within 12 months prior to screening.

Eligibility Criteria

Key Inclusion Criteria: Patients were eligible for enrollment if all the following criteria were met:

1. At least five years of age.
2. Patient had been diagnosed with SCA or sickle β^0 -thalassemia (documented by hemoglobin electrophoresis).
3. The patient had at least two documented episodes of SCC within 12 months of the Screening Visit.
4. If the patient was treated with an anti-sickling agent within three months of the Screening Visit, the therapy must have been continuous for at least three months with the intent to continue for the duration of the study.
5. If female patients of child-bearing potential, agreed to avoid pregnancy during the study and was willing and agreed to practice a recognized form of birth control during the course of the study (e.g., barrier, birth control pills, abstinence).

Exclusion Criteria:

Patients' were ineligible for enrollment if any of the following criteria were met:

1. Patient had a significant medical condition that required hospitalization (other than sickle cell crisis) within two months of the Screening Visit.
2. Patient had prothrombin time international normalized ratio (INR) > 2.0.
3. Patient had serum albumin < 3.0 g/dl.
4. Patient had received any blood products within three weeks of the Screening Visit.
5. Patient had uncontrolled liver disease or renal insufficiency.
6. Patient was pregnant or lactating or had the intention of becoming pregnant during the study.

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

7. Patient was currently taking or had been treated with any form of glutamine supplement within 30 days of the Screening Visit.
8. Patient had been treated with an experimental anti-sickling medication/treatment within 30 days of the Screening Visit (with the exception of hydroxyurea in pediatric patients).
9. Patient was currently taking or had been treated with an investigational drug within 30 days of the Screening Visit (with the exception of hydroxyurea in pediatric patients).
10. Patient was currently enrolled in an investigational drug or device study and/or had participated in such a study within 30 days of the Screening Visit.
11. There were factors that would, in the judgment of the investigator, make it difficult for the patient to comply with the requirements of the study.

Methods

Informed consent was obtained up to four weeks prior to Week 0 (Baseline). Screening procedures were performed anytime between the date of consent and Week 0. Patients were randomized at Week 0 to Endari or placebo in a 2:1 ratio stratified by investigational site and HU use. Randomization information was double blind with un-blinding only permitted if necessitated by a medical emergency.

Treatments Administered

Study subjects received approximately 0.3 g/kg of Endari or placebo (100% maltodextrin) of equivalent volume orally twice daily for 48 weeks. Patient clinic visit occurred every four weeks. After 48 weeks of treatment, the dose was tapered gradually to zero over three weeks. A final evaluation visit occurred two weeks after last dose.

The investigational product, Endari, was provided as a white powder in 5 gram packets. The placebo (maltodextrin) was also packaged as an identically appearing white powder in 5 gram packets. Treatment was not un-blinded for any patient during the study. The study drug dosage for each patient was based on weight with an upper daily limit of 30 grams, as shown in the following schedule:

Table 4: Study GLUSCC09-01 treatment dosage schedule

Weight in kgs.	Weight in lbs.	Per dose in grams	Per day in grams	Packets per dose	Packets per day
<30	<66	5.0	10.0	1	2
30-65	66-143	10.0	20.0	2	4
>65	>143	15.0	30.0	3	6

Source: Study GLUSCC09-01 CSR

Study medications were self-administered by study patients at home. Patients were instructed to mix the powder immediately before ingestion with water or a non-heated beverage other than alcohol, or with a non-heated food such as yogurt, applesauce, or cereal. Mixing L-glutamine with soda or highly acidic juices (such as grapefruit juice or lemonade) was not recommended. Patients were given written and verbal instructions for self-administration of L-glutamine or placebo orally twice daily between 6 am and 9 am and again between 6 pm and 9 pm. A 5-week

Clinical Review

NDA 208587

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supply of study medication was dispensed to the patient at each scheduled monthly visit. Accountability of the used and un-used study medication was recorded.

Throughout the course of the study, clinical and hematological parameters and all adverse events were monitored and reported on an AE eCRF. An AE was defined as any untoward medical occurrence in a clinical investigation in which a patient was administered a pharmaceutical /biological product, regardless of the relationship of the medical occurrence to the pharmaceutical/biological product.

The schedule of study assessments are shown in the table below.

Table 5: GLISCC09-01 - Study Schedule of Assessments

Evaluation	Screening	Treatment Period <i>Study Visits took place every four weeks (± seven days)</i>															End of Study
		Week															
	-4 ¹	0 ²	4	8	12	16	20	24	28	32	36	40	44	48	53	EW	
Informed Consent	X																
Inclusion/Exclusion	X	X															
Medical History	X	X														X ⁶	
Height and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ER/Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Products	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior and Concomitant Procedures/Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Daily Diary Card ³		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Phone Visits ⁴		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC & Retic. Count ⁵	X ¹⁰	X ¹⁰	X	X	X	X	X	X		X		X		X	X	X	
Serum Chemistry ⁵	X															X	
Hepatic Panel ⁵	X															X	
Coagulation Panel ⁵	X															X	
Hb Electrophoresis ⁵	X ⁸																
HIV Test ⁵	X															X ⁷	
Pregnancy Test ^{8,9}	X															X ⁷	
Study Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

¹ Informed consent could be obtained up to four weeks prior to Week 0. The screening assessments could take place any time between Week -4 and Week 0, as long as informed consent had been obtained and all eligibility criteria had been confirmed prior to the Week 0 visit.

² Week 0 was the Baseline visit, the day that patients were enrolled in the study and started L-glutamine or placebo administration.

³ The Daily Diary Card captured dose interruptions, medications, medical facility visits, and adverse events (as recorded by the patients).

⁴ Site personnel contacted the patients between study visits after randomization in order to monitor compliance with the daily diaries and study medication. Telephone visits were conducted on a weekly basis through Week 24 and during the tapering period. They were conducted every other week between Week 24 and Week 48.

⁵ Blood specimens that were drawn during the Screening Visit and all subsequent visits did not require an overnight fast.

⁶ Study participation summary describing course of patient's study participation and status at time of exit from study was required for early withdrawal patients only.

⁷ If necessary, as decided by the principal investigator.

⁸ Only required if results were not available within six months of the Screening Visit date.

⁹ Serum pregnancy tests were performed at the Screening Visit and were administered to all females. If an additional pregnancy test was performed at the Early Withdrawal Visit, either a serum or urine pregnancy test was acceptable.

¹⁰ If the screening laboratory assessments were performed within one week of Week 0 (Baseline), then the Complete Blood Count and Reticulocyte Count did not need to be performed at Week 0 (Baseline).

(Table copied from GLUSCC09-01 CSR -Table 2)

Clinical Review

NDA 208587

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Primary efficacy endpoint: The number of sickle cell crises through Week 48 and prior to start of taper.

A sickle cell crisis was defined as a visit to an emergency room/medical facility for SCD-related pain that was treated with a parenterally administered narcotic or parenterally administered Toradol (ketorolac). The occurrence of chest syndrome (acute clinical pulmonary findings corroborated by findings of a new pulmonary infiltrate on chest X-ray films), priapism, and splenic sequestration were considered sickle cell crises even if the symptoms were not painful enough to require narcotics or Toradol (ketorolac). Splenic sequestration was defined as an increase in spleen size associated with pain in the area of the organ along with a decrease in the hemoglobin concentration of at least 2 g/dL within a 24-hour period.

Secondary efficacy endpoints:

- Number of sickle cell crises at Week 24
- Number of hospitalizations for sickle cell pain at Weeks 24 and 48
- Number of emergency room/medical facility visits for sickle cell pain through Week 24 and through 48 (separately)
- Hematological parameters (hemoglobin, hematocrit, and reticulocyte count)

Safety Endpoints: The incidence of adverse events, safety laboratory results, and vital signs

Reviewer Comment: The primary efficacy endpoint used is appropriate for demonstration of benefit and durability of treatment on disease outcome for the indication sought.

Protocol Amendments

Several amendments to the original protocol were made by the Applicant. A summary of these changes are shown in the table below. Most changes were related to clarifications of study procedures and administrative. The definition of the primary study endpoint of sickle cell crises was revised on four occasions, however any impact of this on the integrity or interpretation of the study results are minimal.

Table 6: Summary of Protocol Amendments

Original Version Date	Amendment Version Date	Key Changes
19 October 2009	28 January 2010	<ul style="list-style-type: none"> • Made change in exclusion criterion • Updated definition of a sickle cell crisis • Corrected sample size calculation from 207 to 220 patients • Clarified that non-compliant patients will not be withdrawn from the study • Added section on additional efficacy analyses • Clarified secondary efficacy endpoint definitions • Added a new section on Central Adjudication Committee
28 January 2010	18 March 2010	<ul style="list-style-type: none"> • Updated inclusion and exclusion criteria • Clarified that serum pregnancy test will be performed for all females at Screening Visit, not just those classified as child bearing potential • Clarified which foods/beverages could be mixed with investigational product • Made change in the definition of primary efficacy endpoint to remove “painful” from the description of sickle cell crises • Added step in emergency unblinding procedure • Provided additional guidance regarding administration of investigational product • Updated supply of investigational product from ‘four’ to ‘five weeks’ • Clarified that all sickle cell disease related events for which patients seek medical attention will be reported as AEs • Updated sample size for both test and placebo groups • Clarified how safety would be monitored during study • Clarified who can perform physical examinations
18 March 2010	16 February 2011	<ul style="list-style-type: none"> • Updated exclusion criteria • Increased number of potential clinical sites • Clarified that screening complete blood count (CBC) and reticulocyte count laboratory values can be used as baseline laboratory, as long as the Screening Visit laboratory was within 1 week of Baseline Visit. • Updated reasons for patient withdrawal • Clarified SAE reporting procedure
16 February 2011	13 September 2011	<ul style="list-style-type: none"> • Revised definition of a sickle cell crisis
13 September 2011	26 March 2012	<ul style="list-style-type: none"> • Increased number of clinical sites from 30 to 35 • Revised definition of a sickle cell crisis

Copied from Study GLUSCC09-01, Clinical Study Report, Table 1.

5.3.2. Study 10478

A Phase II, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-center Study of L-Glutamine Therapy for Sickle Cell Anemia and Sickle β^0 -Thalassemia

This was a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of oral L-glutamine therapy for patients with sickle cell anemia or sickle β^0 -thalassemia who were at least 5 years old.

Clinical Review

NDA 208587

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The primary objective was to evaluate the efficacy of oral L-glutamine in therapy of sickle cell anemia and sickle β^0 -thalassemia as evaluated by the number of occurrences of painful sickle cell crises. The secondary objectives related to efficacy were to assess the effect of oral L-glutamine on frequency of hospitalizations for sickle cell pain, frequency of emergency room visits for sickle cell pain, number of days patients' usual daily activities were interrupted due to sickle cell pain, height and weight, growth curve for patients < 18 years of age, hematological parameters, narcotic usage, alcohol and tobacco use, pain level, energy level, patient activity level, patient appetite, subjective exercise tolerance, and subjective quality of life. Secondary objectives related to safety were to assess L-glutamine in therapy of sickle cell anemia as evaluated by adverse events (AEs), laboratory parameters, and vital signs.

Eligibility criteria

Key Inclusion Criteria

1. Patient was at least 5 years of age.
2. Patient had been diagnosed with sickle cell anemia or sickle β^0 -thalassemia (documented by hemoglobin electrophoresis).
3. Patient had at least 2 episodes of painful crises within 12 months of the screening visit.
4. If the patient had been 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 the next 14 months.
5. If the patient was a female of childbearing potential, she agreed to practice a recognized form of birth control during the course of the study.

Exclusion Criteria

1. Patient had a significant medical condition that required hospitalization (other than sickle painful crisis) within 2 months of the screening visit.
2. Patient had diabetes mellitus with untreated fasting blood sugar > 115 mg/dL.
3. Patient had prothrombin time INR > 2.0.
4. Patient had serum albumin < 3.0 g/dL.
5. Patient had received any blood products within 3 weeks of the screening visit. This criterion was originally within 3 months of the screening visit and was changed to 3 weeks by Amendment #1.
6. Patient had a history of uncontrolled liver disease or renal insufficiency.
7. Patient was pregnant or lactating.
8. Patient had been treated with an experimental anti-sickling medication/treatment (except hydroxyurea) within 30 days of the screening visit.
9. Patient had been treated with an experimental drug within 30 days of the screening visit.

Methods

Informed consent was obtained up to four weeks prior to Week 0. Eligible patients underwent baseline evaluations between the date of consent and Week 0. Patients who met all of the eligibility criteria were randomized (in a 1:1 ratio) to oral L-glutamine at 0.3 g/kg/day or placebo (100% maltodextrin) for 48 weeks. Randomization information was double blinded.

Clinical Review

NDA 208587

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Study visits occurred monthly. After 48 weeks of treatment patients were gradually tapered off study medication over a period of 3 weeks before returning for the final visit at Week 53, 2 weeks after the last dose.

The investigational product and placebo were packaged identically - as a white powder in 5 gram packets. To ensure the blinding of the taste, the powders were to be mixed immediately with a beverage or food before ingestion. Treatment was not un-blinded for any patient during the study. The study drug dosage for each patient was based on weight with increments of 5 grams and an upper daily limit of 30 grams, as shown in the following schedule:

Table 7: Study 10478 treatment dosage schedule

Weight, kg	Weight, lb	Grams Per Dose	Grams Per Day	Packets Per Dose	Packets Per Day
17 - 33.3	37.4 - 73.26	5.0	10.0	1	2
33.4 - 66.6	73.27 - 146.52	10.0	20.0	2	4
> 66.7	> 146.53	15.0	30.0	3	6

Source: Copied from Study 10478 CSR

Patients completed a daily diary card which captured the hospitalizations and emergency room visits, narcotic usage, number of days the patient's usual daily activities were interrupted and maximum daily pain level.

Quality of life was evaluated at Baseline and at Week 24. Quality of life surveys were also administered to patients who were withdrawn from the study prior to completing their study participation. For adults (≥ 18 years of age) the RAND 36-Item Health Survey Questionnaire was used. For patients 5 to 7 years, 8 to 12 years, and 13 to 18 years, separate Peds QL Pediatric Quality of Life Questionnaires were used - the Pediatric Quality of Life Inventory (version 4.0), the Multidimensional Fatigue Scale (standard version), and the Pediatric Pain Questionnaire (standard version).

Concomitant medications were permitted, including other anti-sickling agents. Patients were to note all other medications they took on their daily diary cards. All concomitant medications throughout the study were recorded on the appropriate CRF. It was expected that some patients would require RBC transfusions during the study. If a transfusion became necessary between the screening evaluation and the start of study medication, the patient was considered a screen failure. After 3 weeks the patient could be re-evaluated for possible enrollment (changed from 3 months in protocol amendment version 6/24/2005). If a transfusion became necessary when a patient was taking the study medication, it was recorded on the appropriate CRF.

Primary Efficacy Endpoint: The number of painful sickle cell crises through Week 48 and prior to start of taper.

A painful sickle cell crisis was defined as

- A visit to a medical facility that lasted more than 4 hours (from the date/time of registration to the date/time of departure); and
- The visit was for acute sickling-related pain; and

Clinical Review

NDA 208587

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- The patient was treated with a parenterally administered narcotic (except for facilities in which only orally administered narcotics were used)

The occurrence of chest syndrome (chest-wall pain in association with findings of a new pulmonary infiltrate on chest x-ray films and fever), priapism, and hepatic or splenic sequestration (a sudden increase in liver or spleen size associated with pain in the area of the organ, a decrease in the hemoglobin concentration of at least 2 g/dL, and, for liver sequestration, abnormal change in liver function tests not due to biliary tract disease) was to be considered a crisis; the occurrence of hematuria and exacerbations of pain was not considered a crisis event.

Safety Evaluations

Safety variables in this study included AEs, clinical laboratory evaluations, physical examinations and vital signs. The clinical evaluation at each monthly visit assessed pain, height and weight, average alcohol and tobacco use, energy level, activity level, appetite, and subjective exercise tolerance. Hematological parameters (hemoglobin, hematocrit, and reticulocyte count) were obtained at all visits except Weeks 28, 36, 44, and 53. All AEs were monitored and reported on an AE CRF including a description, onset date, stop date, outcome, frequency, severity, relationship to study medication, action taken regarding study medication, concomitant treatment, and seriousness.

Reviewer Comment: The primary efficacy endpoint used is appropriate for demonstration of benefit and durability of treatment on disease outcome for the indication sought.

Protocol Amendments

Three amendments to the original protocol (dated August 20, 2004) were made by the Applicant. A summary of these changes is shown in the table below.

Date	Amendment
June 24, 2005	<ul style="list-style-type: none">- Exclusion criterion regarding blood products changed from “within 3 months of the screening visit” to “within 3 weeks of the screening visit.”
August 29, 2006	<ul style="list-style-type: none">- The targeted sample size was changed from original plan to randomize approximately 80 patients to “ensure 60 or more evaluable patients for this study” to “ensure that 52 or more patients will complete the study (based on a dropout rate of 30-35%).”- The dropout rate was changed from 15-20% to 30-35% based on the actual withdrawal rates experienced.- Administrative change to name of CRO’s site monitor- A fingertip prick was included as an accepted method of obtaining blood should peripheral venous access not be possible.
September 11, 2006	Administrative change: the name of the Research and Education Institute at Harbor-UCLA Medical Center was changed to LA BioMed.

Review comment: The actual study drop-out rate for Study 10478 was much higher than originally anticipated and may have resulted in under-powering of this study.

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

5.3.3. Legacy Studies

Study 8288 (Niihara, et al 1998; Pilot Study)

Design: This was an open-label, uncontrolled, single-center, pilot study conducted to evaluate the effect of L-glutamine treatment on NAD, NADH and NAD redox potential of sickle RBCs. The effect of L-glutamine supplementation on hematologic parameters, subjective clinical response, and safety was also evaluated.

Study population: Seven subjects (19 to 60 years old) with sickle cell anemia.

Treatment: Study subjects were treated with oral L-glutamine 30 g/day (10 g, TID) for 4 weeks. Blood samples were obtained after overnight fasting at baseline and after 4 weeks of treatment. Follow-up occurred weekly or biweekly to assess compliance and clinical status including AEs.

Results: The total NADH level increased from 47.5 ± 6.3 nmol/mL RBC to 72.1 ± 15.1 nmol/mL RBC ($P < 0.01$), with the NAD redox potential increasing from $47.2 \pm 3.7\%$ to $62.1 \pm 11.8\%$ ($P < 0.01$) in study patients. Clinically, 100% of subjects reported an improvement in overall energy level and a decrease in chronic pain level. Six out of 7 patients reported an increase in activity level and a decrease in narcotics dosage.

Study 8775

Design: This was a Phase 2a, single-center, prospective, randomized, double-blind, placebo-controlled, crossover study designed to evaluate the effect of L-glutamine treatment on total NAD, NAD redox potential, RBC endothelial cell adhesiveness, hematologic parameters, frequency of painful crises, number of hospitalization day, number of painless days, and safety.

Study Population: Subjects (≥ 18 years of age) with a diagnosis of sickle cell anemia that had at least 3 episodes of painful crises during the 12 month period prior to randomization.

Treatment: Subjects were randomized to either oral L-glutamine 30 g/day (10 g, TID) or placebo for 24 weeks, followed by 5 weeks of tapering prior to crossover. Evaluations were done at baseline, weekly or biweekly.

Results: Twenty-four subjects were enrolled, 6 subjects completed the 53 weeks of treatment (double-blind crossover). In the 6 evaluable subjects, there was a significant increase in the number of painless days ($p = 0.00885$). No statistically significant improvement in the number of painful crises was observed ($p = 0.28$). The only AE noted was constipation.

Study 10779

Design: This was an open-label, controlled, single-center study designed to evaluate the effect of L-glutamine treatment on subjects' subjective perception of clinical status, safety, and exercise endurance.

Study Population: Subjects with sickle cell anemia.

Clinical Review

NDA 208587

Endari[®] (L-glutamine)

Treatment: Study subjects were treated with oral L-glutamine 30 g/day for 12 weeks.

There were 2 parts to this study: Part 1- involved an incremental work rate test; Part 2 – involved a constant work rate test where the 80% maximum work rate from the incremental test was utilized. Tests were conducted at baseline and after 8 to 12 weeks of treatment.

Results: Eight out of 14 subjects with sickle cell anemia enrolled completed the study. Seven subjects participated in the exercise endurance studies. Five control subjects were enrolled. The work rates were 88 watts at baseline and 91.5 watts after L-glutamine treatment ($p = 0.18$) for the incremental work protocol; and 5.87 minutes at baseline and 7.27 minutes after treatment ($p = 0.02$) for the constant work protocol.

Study 10511

Design: This was a Phase 2, single-center, prospective, randomized, double-blind, placebo-controlled, parallel-group study conducted to evaluate the effect of L-glutamine treatment on exercise endurance, breath-by-breath exercise response, the incidence of painful crises, level of chronic pain, amount of daily requirement of narcotics, and safety.

Study Population: Subjects (≥ 18 years of age) with sickle cell anemia or sickle β^0 -thalassemia.

Treatment: Subjects were randomized to oral L-glutamine (dose calculated according to subject weight, upper limit of daily dose of 30 g/day) or placebo twice daily. There was a 4-week screening period followed by treatment for 12 weeks and 5-weeks of tapering. Subject visits occurred every 4 weeks; a final evaluation visit occurred 3 weeks after the last dose.

At baseline and then between Weeks 8 and 12, endurance testing utilizing an incremental and a constant work-rate protocol was performed. Lactic acid production and physiological tolerance of exercise were monitored. At each visit the following were recorded: changes in severity and frequency of chronic or acute pain; the type and amount of daily pain medication required; exercise tolerance; and any other clinical aspects or events that occurred including hospitalization or visits to the emergency room. Blood samples were drawn on Day -28 and Day 0 for baseline levels and then at Weeks 4, 8, and 12.

Results: Fifteen subjects were enrolled: 5 subjects were randomized to L-glutamine and 10 were randomized to placebo. AEs were reported for 80% and 70% of subjects in the L-glutamine and placebo groups, respectively. The most commonly reported AE in the L-glutamine group were diarrhea, nausea/vomiting - reported in 40% of subjects. Serious AEs were reported for 40% and 50% of subjects in the L-glutamine and placebo groups, respectively. Sickle cell crisis and hypertension occurred in 20% of L-glutamine treated subjects. No deaths or study withdrawals due to AEs occurred.

Clinical Review

NDA 208587

Endari® (L-glutamine)

6 Review of Efficacy

6.1. Methods

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Clinical Review

NDA 208587

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6.1.1. Trial Design and Endpoints

Studies 10478 and GLUSCC09-01 were both multicenter, double-blind, randomized, placebo-controlled studies designed to evaluate the long-term safety and efficacy of Endari for the treatment of SCD in patients with sickle cell anemia and sickle β^0 -thalassemia who were at least 5 years of age. In both studies, informed consent was obtained up to four weeks prior to Week 0 (Baseline) and screening procedures were performed anytime between the date of consent and Week 0. Patients were randomized at Week 0 to Endari or placebo. In Study GLUSCC09-01, patients were randomized in a 2:1 ratio (Endari: placebo) and randomization was stratified by investigational site and prior hydroxyurea usage (HU; yes/no). In Study 10478, patients were randomized in a 1:1 ratio stratified by investigational site but not by HU use. Randomization was double-blind with un-blinding only permitted if necessary in case of a medical emergency. Each study consisted of a 4-week screening period, a 48-week treatment period, a 3-week tapering period, and a 2-week follow-up period. In both studies, an equivalent volume of oral powder, Endari or placebo, was administered at a dosage of 0.3 g/kg of subject body weight, twice daily for 48 weeks, with an upper limit of 30 g/day for subjects.

Study medications were self-administered by study patients at home. Study visits occurred monthly. After 48 weeks of treatment, patients were gradually tapered off study medication over a period of 3 weeks before returning for the final visit at Week 53, 2 weeks after the last dose. Throughout the course of the study, clinical and hematological parameters and all adverse events (AEs) were monitored and reported. The approved anti-sickling agent, hydroxyurea (HU), was permitted in both studies; however, in GLUSCC0901 randomization was stratified by HU use. All concomitant medications were recorded throughout the course of each study.

In Study 10478, the primary efficacy endpoint was the number of painful sickle cell crises through Week 48 and prior to start of taper. A painful sickle cell crisis was defined as a visit to a medical facility that lasted more than 4 hours (from the date/time of registration to the date/time of departure) for an acute sickling-related pain; treated with a parenterally administered narcotic (except for facilities in which only orally administered narcotics were used). The occurrence of acute chest syndrome (chest-wall pain in association with findings of a new pulmonary infiltrate on chest x-ray films and fever), priapism, and hepatic or splenic sequestration (a sudden increase in liver or spleen size associated with pain in the area of the organ, a decrease in the hemoglobin concentration of at least 2 g/dL, and, for liver sequestration, abnormal change in liver function tests not due to biliary tract disease) was to be considered a crisis; the occurrence of hematuria and exacerbations of pain was not considered a crisis.

Similarly, in Study GLUSCC09-01, the primary efficacy endpoint was the number of sickle cell crises after the first dose of study drug through Week 48 and prior to start of taper. A sickle cell crisis was defined as a visit to an emergency room/medical facility for SCD-related pain that was treated with a parenterally administered narcotic or parenterally administered Toradol (ketorolac). The occurrence of chest syndrome (acute clinical pulmonary findings corroborated by findings of a new pulmonary infiltrate on chest X-ray films), priapism, and splenic sequestration were considered sickle cell crises even if the symptoms were not painful enough to require narcotics or Toradol (ketorolac). Splenic sequestration was defined as an increase in spleen size associated with pain in the area of the organ along with a decrease in the hemoglobin concentration of at least 2 g/dL within a 24-hour period.

Clinical Review

NDA 208587

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Sickle cell crises were classified using a programming algorithm in Study 10478; in Study GLUSCC09-01, an independent central adjudication committee (CAC) determined whether reported sickle cell crises events, as well as hospitalizations and emergency room/medical facility visits related to sickle cell crises, met the criteria for efficacy outcomes. The CAC determinations were considered the primary analysis, with the investigator-reported adverse events analyzed secondarily. There was no central Data and Safety Monitoring Board.

Secondary efficacy endpoints specified for both studies included:

- Number of sickle cell crises at Week 24
- Number of hospitalizations for sickle cell pain through Weeks 24 and 48
- Number of emergency room/medical facility visits for sickle cell pain through Week 24 and 48
- Hematological parameters (hemoglobin, hematocrit, and reticulocyte count) through Weeks 24 and 48

Other exploratory efficacy endpoints included height, weight, and growth curve.

6.1.2. Statistical Analysis Plan

The specified statistical analysis plans and changes to these plans for each individual study are discussed below.

Study 10478

The planned sample size of Study 10478 was based on results from preliminary data and the published literature which showed that the mean number of painful sickle cell crises in a year was 6.5, with a standard deviation of 5.5. The trial was designed to accrue 40 patients per treatment group which would provide 95% power to detect a difference in means of 4.5 (the difference between means of 2.0 for the ENDARI group and 6.5 for the placebo group), assuming a common standard deviation of 5.5 using a t-test with a 0.05 two-sided significance level.

Pre-specified analyses in Study 10478:

The primary efficacy endpoint was the number of sickle cell crises through Week 48 and prior to the start of drug tapering. The treatment groups were to be compared with respect to the number of painful sickle cell crises using an analysis of variance (ANOVA) model with treatment group included as a main effect and controlling for study center.

Key secondary efficacy endpoints were – the number of hospitalizations for sickle cell pain and number of emergency room visits for sickle cell pain through Weeks 24 and 48. Additional exploratory endpoints were specified, as well as safety endpoints, including the incidence of adverse events, safety laboratory results, and vital signs. Secondary efficacy analyses were based on an ANOVA model with treatment group and study center in the model. An interim analysis on the number of painful sickle cell crises through Week 24 was not originally planned, but was included later.

Safety Analyses: No statistical tests were performed for the safety variables, which included AEs, clinical laboratory evaluations, and vital signs.

Clinical Review

NDA 208587

Endari® (L-glutamine)

Applicant's Changes in the Planned Analyses of Study 10478

- Patients from Site 106 (N = 11) were excluded from the primary analyses due to potential scientific misconduct.
- Methods of analysis were changed for the primary parameter as well as the secondary parameters of number of sickle cell crisis through Week 24, number of hospitalizations for sickle cell pain through Week 24 and through Week 48, and number of emergency room visits for sickle cell pain through Week 24 and through Week 48. The change in methods was made to accommodate the unanticipated number of non-completers and therefore the substantial proportion of imputed data. A nonparametric approach was used, the Cochran-Mantel-Haenszel (CMH) test, which was planned for a variety of other secondary parameters.
- The planned missing value imputation method for the primary efficacy analysis was replaced by an alternative method. The original methods were developed anticipating a discontinuation rate of no more than 30%; however, approximately 55% of patients in the full analysis dataset did not complete the study. For discontinued patients with less than 85 days on treatment, the number of crises was imputed by the mean number of crises for the completed patients of the same treatment group. For discontinued patients with 85 days or longer on treatment, the number of crises at Week 48 was imputed by patient according to the individual rate of crises at the date of withdrawal. All imputed values were rounded up to the nearest whole integer. Imputation was documented prior to release of the randomization.
- For analysis of the exploratory endpoint change from baseline in height, due to the high frequency of "0" values the method of analysis was changed from ANOVA to a Wilcoxon two-sample test using the t-approximation.
- The planned analyses of alcohol usage and tobacco usage were not performed because so few patients used either substance.
- Because of the small number of children enrolled, growth curve data and pediatric quality of life (QOL) data were provided in listings but the planned exploratory analyses were not performed.
- Sensitivity analyses were performed for the primary efficacy analysis by imputing values in a more conservative manner. For this analysis, crises following withdrawal were imputed by using the worst case rate from the subset of completed patients regardless of treatment group. This was performed with and without Site 106, for both the full analysis dataset and the PP dataset.

Study GLUSCC09-01

Patients on Study GLUSCC09-01 were assigned to treatment groups in a 2:1 (Endari: placebo) ratio. The study was expected to have a 25% dropout rate. The trial was designed to accrue 220 patients (147 patients assigned to Endari therapy and 73 patients assigned to placebo), which would provide 80% power to detect a difference between the groups in the distribution of the

Clinical Review

NDA 208587

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number of sickle cell crises at Week 48 at a significance level of 0.048 using a two-sided Wilcoxon Rank Sum test. An interim analysis of the number of sickle cell crises through Week 24 was planned to be evaluated at a 0.005 significance level. Both analyses were based on the O'Brien-Fleming method to preserve an overall type I error rate of 0.05. Power calculations were based on testing of the null hypothesis of no difference in the probability distribution of the number of sickle cell crises at Week 48 between the two treatment groups.

Pre-specified analyses in Study GLUSCC09-01:

For the primary endpoint analysis, a non-parametric analytic method – the CMH test, stratified by investigational site and hydroxyurea use, was planned using the rank of the number of sickle cell crises as scores. For patients who discontinue prior to Week 48, sickle cell crisis count was to be imputed using the mean number of crises for the patients of the same treatment group who did complete Week 48; if the imputed count was less than the crisis count at the time of discontinuation, the latter was to be used.

Secondary endpoints included the number of sickle cell crises at Week 24; number of hospitalizations for sickle cell pain at Weeks 24 and 48; number of emergency room/medical facility visits for sickle cell pain through Week 24 and through 48 (separately); and hematological parameters (hemoglobin, hematocrit, and reticulocyte count). The safety endpoints were the incidence of adverse events, safety laboratory results, and vital signs.

One interim analysis was pre-specified and performed when 80 patients had completed 24 weeks of the study and had taken at least 50% of medication during that time. A flexible fixed-sequence testing method was specified to be performed at the 0.005 significance level for the interim analysis after discussion with FDA. The significance level for the final analysis depended on the acceptance or rejection of the null hypothesis of the interim analysis. In the final analysis only the significance level for the primary endpoint, the number of sickle cell crises at Week 48, was adjusted (0.045 was allocated) as described above.

The same non-parametric method described above for the primary efficacy endpoint analysis was to be used for the analysis of the key secondary endpoints, with the exception of the hematological parameters. For patients who discontinue prior to Week 48, counts were to be imputed in the same manner described for the primary efficacy; for the 24-week time point the imputed count was to be based on the mean number of events for the patients of the same treatment group who did complete Week 24. Pooling of low-enrolling investigational sites was planned prior to unblinding.

Applicant's Changes in the Planned Analyses in Study GLUSCC09-01

- While randomization was stratified by study site and baseline hydroxyurea use, efficacy analyses control for the region of study site.
- The specified method for comparing distributions of sickle cell crisis events between treatment arms was the stratified Wilcoxon Rank Sum Test. Originally, the Applicant submitted a primary efficacy result that used a CMH test with the option "SCORES = RANK" specified, instead of the intended "SCORES = MODRIDIT" option. The CMH test with modified ridit scoring is an equivalent method to the stratified Wilcoxon Rank Sum Test as used for the sample size calculation.

Clinical Review

NDA 208587

Endari® (L-glutamine)

- The list and hierarchy of secondary efficacy endpoints changed between the submission of the interim analysis (at Week 24) and the final Clinical Study Report and Integrated Summary of Efficacy Report. Originally, the key secondary efficacy endpoints were specified as the interim analysis of sickle cell crises through Week 24, the number of hospitalizations through Weeks 24 and 48, and the number of ER visits through Weeks 24 and 48. The Clinical Study Report included unplanned analyses of the time to first sickle cell crisis and time in hospital.

6.2. Study Population

Baseline Demographic and Clinical Characteristics

There were a total of 81 patients enrolled in Study 10478, 42 patients were randomized to the Endari arm and 39 patients to the placebo arm. One study site was suspected by the Applicant of potential misconduct; as a result, data for 11 patients enrolled at this site are omitted throughout this review, leaving 70 patients. In Study GLUSCC09-01, a total of 230 patients were enrolled across 31 study sites, with 152 patients randomized to treatment with Endari compared to 78 patients randomized to placebo treatment. Patient characteristics at baseline were mostly similar between arms in each study. Patient age at baseline ranged from 5 years to 58 years in Study GLUSCC09-01; in Study 10478, patient age at baseline ranged from 9 to 58. Study 10478 enrolled mostly adults, whereas Study GLUSCC09-01 enrolled a balance of pediatric and adult patients in each treatment arm. There were no patients over the age of 65 years in either study. While overall enrollment was balanced by sex in Study 10478, the ratio of female to male patients was imbalanced across treatment groups; more than two-thirds of patients were female in the Endari arm, and approximately one-third of patients were female in the placebo arm. In both treatment arms of Study GLUSCC09-01, a slightly higher number of female patients were enrolled. In both studies, the majority of patients in the study were black. The average baseline weight and height of patients was comparable between treatment groups in both studies.

At study entry in Study GLUSCC09-01 about 67% of patients in both the Endari arm and the placebo arm had been taking hydroxyurea for at least three months prior to enrollment. In Study 10478 about 62% of patients in the Endari arm were on hydroxyurea at baseline compared to about 39% of patients in the placebo arm among all patients treated (Endari, 37; placebo, 33). In Study 10478, the imbalance in rates of hydroxyurea use at baseline between treatment groups may be attributable to the fact that this study did not stratify randomization by hydroxyurea use. Both studies stratified randomization by study site; as a result, the number of patients enrolled at each site was well balanced between treatment arms. Additionally, all patients were enrolled in sites located in the United States.

In Study GLUSCC09-01 the mean number of sickle cell crises per protocol per patient during prior year at study entry was 3.9 in the Endari arm (median, 3.0; range 0-16) and 4.1 in the placebo arm (median, 3.0; range 0-18). In Study 10478, number of crises during prior year was

Clinical Review

NDA 208587

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captured by yes/no answer to the question, ‘Has the patient had at least two episodes of painful crises within the last 12 months?’

Baseline characteristics of the patients from both studies are further summarized in the table below.

Table 8: Baseline Demographic and Clinical Characteristics by Study and Treatment Group

Variable	Study 10478		Study GLUSCC09-01	
	Endari (N = 37)	Placebo (N = 33)	Endari (N = 152)	Placebo (N = 78)
Age, in years				
Mean (SD)	29.8 (10.7)	27.2 (10.2)	22.4 (12.3)	21.4 (12.4)
Range	(11 – 58)	(9 – 55)	(5 – 57)	(5 – 58)
Age group [%, (N)]				
≤18	13.5 (5)	15.2 (5)	49.3 (75)	55.1 (43)
>18	86.5 (32)	84.8 (28)	50.7 (77)	44.9 (35)
Sex [%, (N)]				
Female	66.7 (22)	34.5 (10)	52.0 (79)	57.7 (45)
Male	33.3 (11)	65.5 (19)	48.0 (73)	42.3 (33)
Race/Ethnicity [%, (N)]				
Black	97.0 (32)	96.6 (28)	94.7 (144)	93.6 (73)
Hispanic	3.0 (1)	3.4 (1)	2.6 (4)	3.8 (3)
Other	---	---	2.6 (4)	2.6 (2)
Weight, in kg				
Mean (SD)	64.5 (14.2)	68.2 (17.2)	57.9 (20.3)	55.5 (20.7)
Range	(28.3 – 98.0)	(37.6 – 114.3)	(17.5 – 109.1)	(17.7 – 120.9)
Height, in cm				
Mean (SD)	167.7 (10.3)	168.4 (10.7)	160.2 (18.1)	157.5 (17.0)
Range	(138 – 190.5)	(135 – 193.0)	(106 – 192)	(113 – 187)
Hydroxyurea Use [%, (N)]				
Yes	57.1 (24)	38.5 (15)	67.1 (102)	66.7 (52)
No	42.9 (18)	61.5 (24)	32.9 (50)	33.3 (26)
Site/Region [%, (N)]				
101	28.6 (12)	30.8 (12)	---	---
102/103	26.2 (11)	28.2 (11)	---	---
107	45.2 (19)	41.0 (16)	---	---
Midwest	---	---	9.9 (15)	12.8 (10)
Northeast	---	---	31.6 (48)	29.5 (23)
South Atlantic	---	---	27.0 (41)	26.9 (21)
South Central	---	---	13.8 (21)	14.1 (11)
West	---	---	17.7 (27)	16.7 (13)
Baseline crisis count				
Mean (SD)	---	---	3.9 (2.7)	4.1 (2.8)
Range	---	---	(0 – 16)	(1 – 18)

SOURCE: FDA Table derived from Table 12 of Applicant’s [Integrated Summary of Efficacy](#)

Patient Disposition

Among the 70 patients (N = 37, Endari; N = 33, Placebo) in Study 10478, more than half of patients withdrew from the study before the full evaluation period (57.1%, N = 40; 51% and 64% for Endari and placebo arm, respectively). The most frequently cited reasons for early withdrawal in both treatment arms were “Non-compliance”, “Consent withdrawn”, and “Other”.

Clinical Review

NDA 208587

Endari® (L-glutamine)

Overall, about 32% of the 230 enrolled patients dropped out of Study GLUSCC09-01 before the full 48-week treatment period, with a higher dropout rate among patients randomized to the Endari arm (36%) compared to the placebo arm (24%). The most commonly reported reasons for early withdrawal in both treatment arms were “Consent withdrawn” and “Other”. In both studies, these descriptions and additional information collected do not provide sufficient detail as to whether study dropout was related to the patient’s assigned treatment group. Across both studies, three patients died before the end of the study treatment period. All three subjects who died were randomized to the Endari arm in their study; however, there is no information to suggest that their deaths were related to their assigned treatment. No autopsies were performed on these patients.

The following table further summarizes patient disposition across both studies.

Table 9: Patient Disposition, by Study and Treatment Group

N (%)	Study 10478		Study GLUSCC09-01	
	Endari (N = 37)	Placebo (N = 33)	Endari (N = 152)	Placebo (N = 78)
Completed study	18 (48.6)	12 (36.4)	97 (63.8)	59 (75.6)
Withdrawn	19 (51.4)	21 (63.6)	55 (36.2)	19 (24.4)
Reason for early termination				
Consent withdrawn	3 (8.1)	5 (15.2)	23 (15.1)	9 (11.5)
Noncompliance	9 (24.3)	9 (27.3)	8 (5.3)	1 (1.3)
Lack of efficacy	0	1 (3.0)	---	---
Lost to follow-up	2 (5.4)	1 (3.0)	5 (3.3)	3 (3.8)
Adverse events	0	1 (3.0)	5 (3.3)	0
Death	1 (2.7)	0	2 (1.3)	0
Initiation of alternative anti-sickling agent	---	---	1 (0.7)	0
Other	4 (10.8)	4 (12.1)	11 (7.2)	6 (7.7)

SOURCE: Table 13 of Applicant’s [Integrated Summary of Efficacy](#)

Table 10: Percent of patients (N) remaining on study by 12-week intervals and Days on study, by study and treatment group

	Study 10478		Study GLUSCC09-01	
	Endari (N = 37)	Placebo (N = 33)	Endari (N = 152)	Placebo (N = 78)
Baseline Visit	100% (37)	100% (33)	100% (152)	100% (78)
Week 12	81.1% (30)	75.8% (25)	88.2% (130)	93.6% (72)
24	67.6% (25)	66.7% (22)	75.7% (112)	85.9% (67)
36	51.4% (19)	45.5% (15)	69.1% (107)	82.1% (62)
48	48.6% (18)	36.4% (12)	63.8% (97)	75.6% (55)
Days on study, median (min, max)	364 (49, 394)	280 (36, 430)	368 (2, 449)	372 (29, 442)

SOURCE: FDA Reviewer Analysis, Adapted from Table 5 of Applicant’s [Study GLUSCC09-01 Clinical Study Report](#)

To further understand the amount of time patients spent on either study, the table above summarizes patient attrition by 12-week intervals as well as the median number of days spent on the study by treatment group. Overall, half of patients in Study 10478 randomized to Endari treatment spent at least 320.5 days (about 46 weeks) on the study, compared to a median of 224 days (32 weeks) among placebo patients. In Study GLUSCC09-01, the median number of days on study was similar between treatment arms. Patients who dropped out early from either study

Clinical Review

NDA 208587

Endari® (L-glutamine)

had less exposure to their assigned treatment; because dropout rates were differential across both studies, it is difficult to assess the potential treatment effect of Endari. Although reasons given for study withdrawal are not sufficiently informative, the fact that dropout differs by treatment group in both studies suggests that missing data are not missing at random. This assumption has a wide impact on the choice of approach used to handle incomplete data (e.g., imputation), as well as the choice of analytic method to assess the treatment effect. Most analytic methods are asymptotically valid under the “missing at random” assumption, but not under the assumption that data are “missing not at random”.

Protocol Violations

There were a few instances of protocol violations in both studies. In some cases, patients were enrolled who did not meet the inclusion criteria of having experienced at least two sickle cell crises in the year prior to study enrollment. Additionally, a few patients were enrolled who were not diagnosed with sickle cell anemia or sickle β^0 -thalassemia.

6.3. Results

Efficacy results from Studies 10478 and GLUSCC09-01 are not considered to be comparable, due to differences in the definitions and classification of the primary endpoint, the number of sickle cell crises experienced through Week 48 of treatment. Patients in Study 10478 experienced a wider range of crises within the 48-week treatment period (0 to 90 crises) compared to patients in Study GLUSCC09-01 (0 to 15 crises). Study GLUSCC09-01 randomized patients in a ratio of 2:1 to Endari vs. placebo treatment, while Study 10478 randomized patients to assigned treatment groups in a 1:1 ratio. Randomization in Study GLUSCC09-01 was stratified by study site and baseline hydroxyurea use; in Study 10478, randomization was stratified only by study site. Additionally, early study dropout was high and differential between treatment arms in both studies; more than half of patients enrolled in Study 10478 dropped out of the study before the full 48-week treatment period. For these reasons, the Agency reviewed efficacy results separately for each study.

Efficacy Results – Primary Endpoint

Efficacy results from both studies are summarized in the table below.

Study 10478 did not meet its specified significance level for its primary efficacy analysis. The Applicant originally submitted a primary efficacy analysis for Study GLUSCC09-01 that used a statistical test (CMH with rank scoring) that was different than what was intended and specified. The Applicant later submitted a “re-analysis” of the primary efficacy endpoint which FDA accepted as the specified primary efficacy analysis (CMH with modified ridit scoring). While, the primary efficacy analysis in Study GLUSCC09-01 was statistically significant in favor of Endari treatment, concerns with high and differential study dropout rates and the imputation method used by the Applicant make the finding difficult to interpret. Additionally, the interim

Clinical Review

NDA 208587

Endari® (L-glutamine)

analysis of was not significant as a key secondary endpoint; p-values for secondary endpoints listed in the table are considered nominal.

Table 11: Primary Efficacy Analysis, Number of sickle cell crises, by Study and Treatment group

Parameter	Study 10478		Study GLUSCC09-01	
	Endari (N = 33)	Placebo (N = 29)	Endari (N = 152)	Placebo (N = 78)
Primary Analysis				
Mean (SD)	4.5 (5.37)	10.8 (18.74)	3.2 (2.25)	3.9 (2.53)
Median (min, max)	4 (0, 27)	5 (0, 90)	3 (0, 15)	4 (0, 15)
p-value (controlling for study center)		0.072		---
p-value (controlling for region and HU use)		---		0.0630
p-value (Applicant re-analysis*)		---		0.0052

*In the Integrated Summary of Efficacy, the Applicant submitted a “re-analysis” of the primary efficacy endpoint in Study GLUSCC09-01

SOURCE: Table 14 of Applicant’s [Integrated Summary of Efficacy](#)

Because of high and differential dropout rates in Study GLUSCC09-01, the CMH test is not the optimal analytic method to compare the distribution of sickle cell crisis counts between treatment groups. The Applicant’s imputation method assigned a crisis count of 3 to any patients from the Endari treatment group who dropped out of the study early having experienced fewer than 3 crises, and a crisis count of 4 was assigned to placebo patients who dropped out of the study early having experienced fewer than 4 crises. These imputed values represent the rounded average crisis count among patients in the assigned treatment group who completed the 48-week treatment period. Any patients who dropped out of the study early with more than the average crisis count among completers from their treatment group did not have an imputed value; their crisis count at time of dropout was carried forward as their count through 48 weeks. This method of imputation may have introduced bias in the primary and secondary efficacy results.

To further examine the impact of how incomplete crisis counts were handled, FDA considered four possible patient experiences as represented in the dataset of Study GLUSCC09-01, listed in the table below. These four groups are mutually exclusive and comprise the full study population. For data to be entered into the Applicant’s analysis database a patient had to have experienced a qualifying crisis event; as a result, all “missing” crisis count values were assumed as having a value of zero. Of the 230 patients enrolled in the study, there were 137 patients across both treatment groups who completed 48 weeks of treatment and had at least one crisis event recorded; this is represented in the first row of the table below. There were 19 other patients who completed the study but did not have any crisis events recorded (Row 2 of the table); in this case, it is reasonable to assume that if no crisis event was recorded then no crisis event was experienced. This was explained by the Applicant in response to a request for information from FDA. FDA analyses assume that the final crisis count was zero for patients having such records. For patients who did not complete the study, however, it is not clear from study documentation whether non-completers with no recorded crisis counts have a count equal to zero, missing, or unknown. Thus, an FDA sensitivity analysis population consists of the first three rows of the table below, which represent 206 patients who completed at least 48 weeks of treatment or had at least one crisis recorded at their time of dropout as well as a population that

Clinical Review

NDA 208587

Endari® (L-glutamine)

relies on multiple imputation methods to impute counts for 24 patients who did not complete the study and had no crises recorded.

Table 12: FDA Exploratory Analysis: Patient Experiences on Study GLUSCC09-01, Number (%) of patients by study experience

Study Experience	Endari (N = 152)	Placebo (N = 78)
Completed study; at least one crisis recorded	82 (53.9)	55 (70.5)
Completed study; no crises recorded	15 (9.9)	4 (5.1)
Did not complete study; at least one crisis recorded	35 (23.0)	15 (19.2)
Did not complete study; no crises recorded	20 (13.2)	4 (5.1)
Total	152	78

SOURCE: FDA Reviewer Analysis

The table below displays the distribution of observed (non-imputed) sickle cell crisis counts in each treatment group. Crisis counts ranged from 0 to 15, and the crisis counts were not normally distributed in either group; given this information, using the average crisis count among completers to impute an incomplete crisis count is concerning. The Applicant's imputation method changes the shapes of the distributions of the number of sickle cell crises in each treatment group because of the high number of three's and four's imputed for Endari and placebo non-completers, respectively. Additionally, the imputation method does not take into account other characteristics, such as time spent on the study, or study stratification factors which, when controlled for in the primary efficacy analysis, seem to be associated with the study outcome. The distribution of crises in both treatment groups in the FDA sensitivity analysis population more closely resembles the ITT population with no imputed counts.

Table 13: Exploring the impact of the Applicant's imputation method on the distribution of sickle cell crisis events by treatment group

Number of Crises (Cumulative Percentage)	FDA sensitivity analysis population		ITT population, Applicant's Imputation Rule	
	Endari N = 132	Placebo N = 74	Endari N = 152	Placebo N = 78
0	15 (11.4)	4 (5.4)	15 (9.9)	4 (5.1)
1	36 (38.6)	12 (21.6)	16 (20.4)	10 (17.9)
2	23 (56.1)	15 (41.9)	17 (31.6)	11 (32.1)
3	16 (68.2)	8 (52.7)	62 (72.4)	4 (37.2)
4	16 (80.3)	9 (64.9)	16 (82.9)	23 (66.7)
5	8 (86.4)	12 (81.8)	8 (88.2)	12 (82.1)
6	6 (90.9)	5 (87.8)	6 (92.1)	5 (88.5)
7	5 (94.7)	4 (93.2)	5 (95.4)	4 (93.6)
8	2 (96.2)	2 (95.9)	2 (96.7)	2 (96.2)
9	3 (98.5)	1 (97.3)	3 (98.7)	1 (97.4)
10	0	0	0	0
11	1 (99.2)	1 (98.6)	1 (99.3)	1 (98.7)
12	0	0	0	0
13	0	0	0	0
14	0	0	0	0
15	1 (100)	1 (100)	1 (100)	1 (100)

SOURCE: Applicant's Integrated Summary of Efficacy, Tables 1.2; FDA Reviewer Analysis

Figure 1: FDA Analysis: Distribution of sickle cell crisis events by treatment group, FDA sensitivity analysis population, N=206

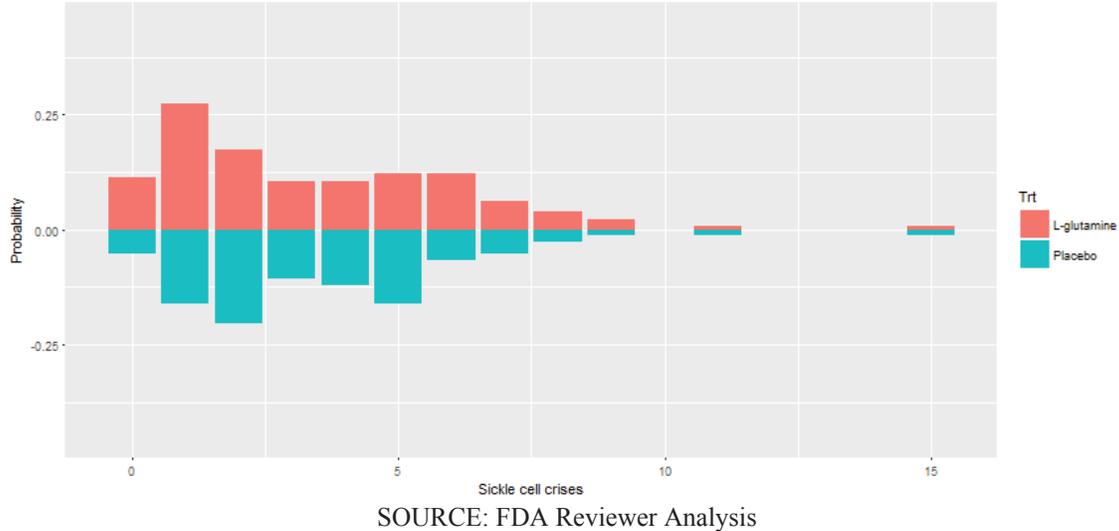
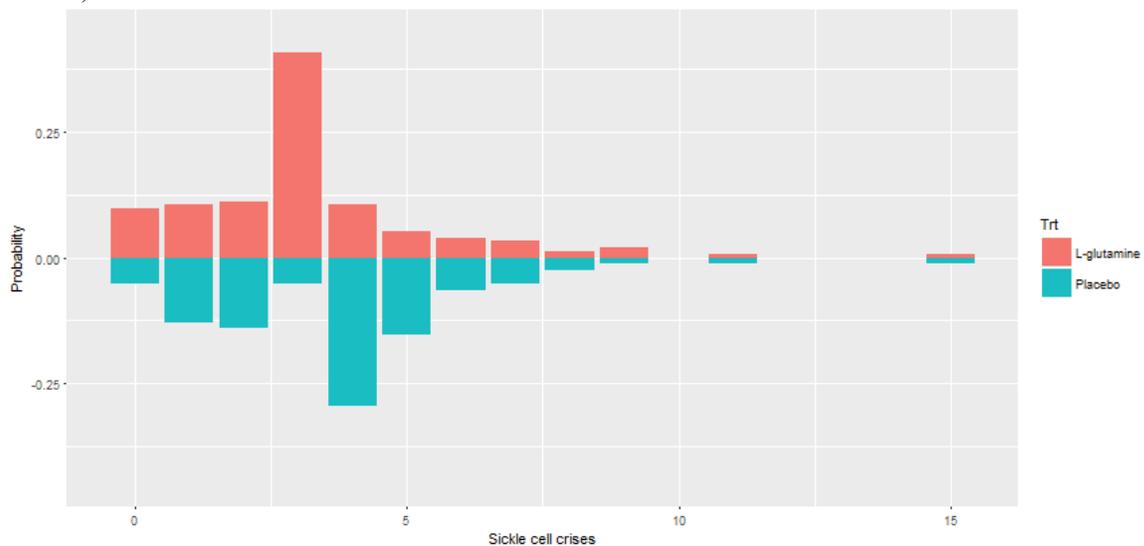


Figure 2: Distribution of sickle cell crises by treatment group under Applicant's imputation rule, ITT population, N=230



To assess the impact of the originally specified imputation scheme, the Applicant submitted two additional imputation methods: Last observation carried forward (LOCF), and Time-adjusted LOCF. Using the LOCF method, the crisis count for any patient who did not complete the 48-week treatment period was estimated by their last known crisis count before dropping out of the study. The Applicant's Time-adjusted LOCF method estimates the crisis count at 48 weeks for patients who dropped out early using the number of events at the time of discontinuation divided by the number of days on study medication multiplied by 336. While the Time-adjusted LOCF method attempts to account for time spent on the study, it makes a difficult to justify assumption that the timing between crises takes on a linear trend. In both cases, neither the mean nor median number of crises is an appropriate measure to summarize the data.

Table 14: Applicant Analyses: Number of sickle cell crises (SCC) by methods of imputation

Clinical Review
 NDA 208587
 Endari® (L-glutamine)

	Endari N=152	Placebo N=78
Summary of SCC distribution using Applicant's specified imputation method*		
Mean (SD)	3.2 (2.24)	3.9 (2.54)
Median (min, max)	3 (0, 15)	4 (0, 15)
Alternative imputation method 1: Last observation carried forward (LOCF)		
Mean (SD)	2.5 (2.56)	3.5 (2.74)
Median (min, max)	2 (0, 15)	3 (0, 15)
Alternative imputation method 2: Time-adjusted LOCF		
Mean (SD)	3.6 (4.34)	6.8 (19.09)
Median (min, max)	2 (0, 28)	4 (0, 168)

*Applicant's primary efficacy analysis: CMH test with modified ridit scores, controlling for study stratification factors, nominal p-value=0.0052

SOURCE: Applicant's Integrated Summary of Efficacy, Post Text Tables 4.2 and 5.2

The table above compares each of the alternative imputation methods to the Applicant's original primary efficacy analysis. In each case, both the mean and the median number of crises in the Endari treatment group are lower than in the placebo group, though the magnitude of the difference between treatment groups varies. Given the amount and differential rate of early study dropout as well as the methods used by the Applicant to impute incomplete sickle cell crisis event counts, the analytic method used by the Applicant may not be the appropriate test to demonstrate the benefit of Endari treatment to reduce the occurrence of crisis events among patients with sickle cell disease. The protocol-specified analyses proposed by the Applicant rely on assumptions about the completeness and quality of study data that may not have been met. Since the rate of early dropout may be related to assigned treatment group, time spent on the study, site location, and baseline hydroxyurea use and other unknown factors, interpretation of the primary efficacy analysis as originally specified is difficult.

One drawback of the CMH test used by the Applicant is that it ranks the number of crises (according to the Applicant's imputation method) by treatment group and stratification factors without accounting for time patients spent on the study; this complicates interpretation of the primary efficacy results considering that patients from both treatment arms dropped out of the study early, with more Endari patients exiting the study early compared with placebo patients as well as more Endari patients not taking hydroxyurea at baseline withdrawing early compared to other patients.

FDA Data Assessment

An alternative analysis was performed by FDA in an effort to overcome the difficulties caused by the incomplete data records. A recurrent event analysis based on the proportional rate regression model (Lawless and Nadeau, 1995; Lin et al., 2000) was performed by FDA to incorporate information on patients' time spent on study and to take into account the fact that times between crisis events for a patient are not necessarily independent. Covariances for the estimators of the regression parameters $\hat{\beta}$, accounting for the dependence structure of the recurrence times, can be computed using a robust (or sandwich) estimator. In this analysis, there

Clinical Review

NDA 208587

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is no need for imputation of incomplete crisis counts and all events (as well as timing of events) are included. Patients without any events were censored at their last visit. Based on this analysis, FDA obtained a hazard ratio of 0.73 (95% CI: [0.55, 0.99]) in favor of the ENDARI treatment group. In the figure below, mean cumulative numbers of crises up to time t (in weeks) is plotted (Nelson, 2003), which is analogous to the Nelson-Aalen estimator for the cumulative hazard function of time to event data. The estimated SCC counts at 48 weeks are 3.8 (95% CI: [3.1, 4.5]) and 3.0 (95% CI: [2.5, 3.4]) for patients in the placebo and Endari and treatment groups, respectively.

Figure 3: FDA Analysis: Mean cumulative functions for sickle cell crisis events by treatment group

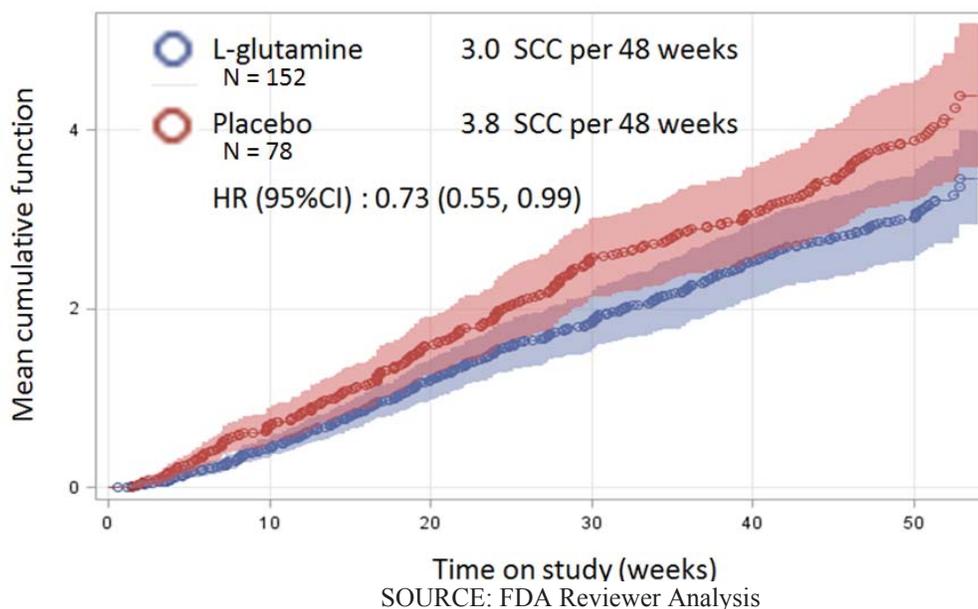


Figure 4: FDA Analysis: Estimated 48-week sickle cell crisis event count by treatment group, recurrent event analysis, ITT population (N = 230)

	Endari (N = 152)	Placebo (N = 78)
Estimated sickle cell crisis event count (95% CI)	3.0 (2.5, 3.4)	3.8 (3.1, 4.5)
Hazard Ratio, Endari vs. Placebo (95% CI)	0.73 (0.55, 0.99)	

SOURCE: FDA Reviewer Analysis

The FDA analysis of sickle cell crises as recurrent events takes relevant study information into account to compare the number of crises between treatment groups at Week 48 without requiring imputation of incomplete data, although the analysis requires an assumption of independent censoring. Overall, the result favors Endari treatment over placebo.

Sensitivity analyses were performed by FDA using negative binomial regression (NBR), taking into account time spent on study and not requiring imputation of incomplete crisis counts, to compare rates of crises per 48 weeks between treatment groups. First, a NBR analysis was performed using the FDA sensitivity analysis population described previously where incomplete crisis counts for 24 patients (see table above summarizing patient experiences on Study

Clinical Review

NDA 208587

Endari® (L-glutamine)

GLUSCC09-01) were omitted. A second FDA analysis using NBR assumes that incomplete counts for the 24 patients not completing the study were zeros. Finally, a multiple imputation approach, using fully conditional specification (FCS; van Buuren, 2012), imputes counts for the 24 patients excluded from the FDA sensitivity analysis population, taking into account the patient’s assigned treatment group, study site, baseline hydroxyurea use, duration of time on study, age, and baseline crisis count to impute incomplete crisis counts. Results of each of the FDA sensitivity analyses using NBR vary due to different assumptions made about incomplete crisis counts among 24 patients who did not complete the study. Together, these exploratory analyses can be interpreted as showing a modest trend supporting a claim of benefit for Endari.

Table 15: FDA Exploratory Analyses: Rates of sickle cell crisis counts per 48 weeks between treatment groups, Negative binomial regression

FDA Analysis Set	Endari (N = 132)	Placebo (N = 74)	Rate Ratio for Endari vs. Placebo [95% CI]
FDA sensitivity analysis population (data consisting of rows 1-3 of Table 12 above) (95% CI), N=206	3.3 (2.8, 3.8)	4.1 (3.3, 4.9)	0.80 [0.64, 1.01]
ITT population, assuming crises counts for row 4 in Table 12 are “0” (95% CI), N = 230	3.3 (2.7, 3.9)	4.2 (3.4, 5.1)	0.77 [0.61, 0.99]
Multiple imputation for crises counts in row 4 of Table 12 using fully conditional specification*, ITT population (95% CI), N=230	3.9 (3.3, 4.5)	4.3 (3.2, 5.4)	0.91 [0.73, 1.12]

All analyses use time on study as an offset and control for study stratification factors (region of study site and baseline hydroxyurea use)

*Multiple imputation approach imputes crisis counts for 24 patients using information on treatment group, study stratification factors, time on study, baseline age, and baseline crisis count

SOURCE: FDA Reviewer Analyses

Listed in the table below are two sensitivity analyses considered by the Applicant using negative binomial regression. These analyses also demonstrate a marginal benefit of Endari treatment over placebo, even when taking into account the number of crises experienced by the patient in the year prior to study enrollment. The analysis in the first row of the table is nearly identical to the second FDA analysis in the table above. The Applicant also submitted several analyses based on single and multiple imputation approaches, and using various regression models.

Table 16: Applicant sensitivity analyses of the primary efficacy endpoint using negative binomial regression, comparing rates of sickle cell crisis events per 48 weeks

Applicant Analysis Set	ENDARI (N = 152)	Placebo (N = 78)	Rate Ratio for ENDARI vs. Placebo [95% CI]
ITT population (95% CI), N=230	3.3 (2.7, 3.8)	4.2 (3.4, 5.1)	0.78 [0.61, 0.99]
ITT population, model also adjusting for previous year’s crises (95% CI), N=230	3.2 (2.7, 3.7)	4.0 (3.3, 4.9)	0.79 [0.63, 0.99]

Each model includes time on study as an offset, controlling for study stratification factors

SOURCE: Applicant’s Response to FDA Statistical Information Request

Clinical Review

NDA 208587

Endari® (L-glutamine)

It is important to note that there is no ideal post-hoc analysis that can overcome the amount and differential nature of study dropout in Study GLUSCC09-01. There is no optimal imputation approach or analytic method that can estimate the true 48-week sickle cell crisis counts of patients who dropped out of the study early. The analyses presented here represent a spectrum of assumptions that can be made about the observed data. They are meant to show that, when incomplete crisis counts are handled differently than the Applicant's method and analysis of the primary efficacy endpoint takes time on study into account to compare rates of crises between treatment groups after 48 weeks of treatment, the results trend in favor of Endari. However, in some cases, upper limits of confidence intervals for rate ratios comparing treatment groups include a ratio of 1.

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoints specified for both studies included the number of sickle cell crises through Week 24, as well as the number of hospitalizations and the number of emergency room (ER) visits at Weeks 24 and 48. In both studies, the interim analysis of the primary efficacy endpoint did not reach specified levels of significance (0.005); thus p-values for these endpoints and additional secondary endpoints are considered nominal. Additionally, these analyses were performed on data that included imputed values of incomplete crisis counts according to individual study CSR imputation rules. As with the primary efficacy analysis, the imputation methods may have introduced bias in secondary efficacy results. In the ISE, the Applicant omitted the interim analysis from the planned statistical analyses, and did not present interim results that were included in individual study CSRs.

Table 17: Secondary efficacy results, by Study and Treatment group

Parameter	Study 10478		Study GLUSCC09-01	
	Endari (N = 33)	Placebo (N = 29)	Endari (N = 152)	Placebo (N = 78)
Number of Sickle Cell Crises Through Week 24				
Mean (SD)	2.5 (2.55)	5.5 (8.46)	1.7 (1.58)	2.1 (1.69)
Median (min, max)	2 (0, 12)	3 (0, 38)	2 (0, 8)	2 (0, 7)
Nominal p-value (controlling for study center)	0.060		---	
Nominal p-value (controlling for region and HU use)	---		0.169	
Number of Hospitalizations Through Week 24				
Mean (SD)	0.8 (1.18)	1.3 (1.42)	1.2 (1.27)	1.6 (1.47)
Median (min, max)	1 (0, 5)	2 (0, 5)	1 (0, 6)	2 (0, 6)
Nominal p-value (controlling for study center)	0.036		---	
Nominal p-value (controlling for region and HU use)	---		0.070	
Number of ER Visits Through Week 24				
Mean (SD)	1.9 (2.71)	4.7 (9.02)	0.8 (1.26)	0.8 (1.23)
Median (min, max)	1 (0, 12)	2 (0, 40)	0 (0, 10)	0 (0, 7)
Nominal p-value (controlling for study center)	0.105		---	
Nominal p-value (controlling for region and HU use)	---		0.833	

Clinical Review

NDA 208587

Endari® (L-glutamine)

use)				
Number of Hospitalizations Through Week 48				
Mean (SD)	1.5 (2.46)	2.3 (2.42)	2.3 (1.99)	3.0 (2.31)
Median (min, max)	1 (0, 10)	2 (0, 10)	2 (0, 14)	3 (0, 13)
Nominal p-value (controlling for study center)		0.072		---
Nominal p-value (controlling for region and HU use)		---		0.041
Number of ER Visits Through Week 48				
Mean (SD)	3.7 (5.63)	9.4 (19.91)	1.1 (1.49)	1.6 (2.30)
Median (min, max)	2 (0, 27)	3 (0, 94)	1 (0, 12)	1 (0, 15)
Nominal p-value (controlling for study center)		0.129		---
Nominal p-value (controlling for region and HU use)		---		0.128

SOURCE: [Study 10478 CSR Tables 11-3 and 11-4](#); [Study GLUSCC09-01 CSR Tables 6 and 10](#)

Hematological parameters were also specified as secondary endpoints in Study GLUSCC09-01, and are summarized in the Study GLUSCC09-01 CSR. Also, there were additional endpoints for which unplanned analyses were performed – Incidence of ACS, Time to First Sickle Cell Crisis and Cumulative Time in Hospital through Week 48. There were 2 occurrences of ACS in Study 10478, so no analyses were performed on this endpoint. Results for additional unplanned secondary endpoints in Study GLUSCC09-01 are summarized below.

Table 18: Unplanned secondary efficacy endpoint: Incidence of Acute Chest Syndrome in Study GLUSCC09-01, by Treatment Group

Endpoint	Study GLUSCC09-01	
	Endari (N = 152)	Placebo (N = 78)
Incidence of Acute Chest Syndrome		
Mean (SD)	0.1 (0.37)	0.3 (0.63)
Median (min, max)	0 (0, 2)	0 (0, 3)
Nominal p-value (controlling for region and HU use)	0.0028	

SOURCE: Applicant's [Integrated Summary Efficacy Table 21](#)

In Study GLUSCC09-01, the incidence of ACS was lower among patients randomized to Endari compared to placebo; since overall incidence of ACS was low in the study, these results should be interpreted with caution.

Time to first sickle cell crisis was also examined in the Applicant's ISE graphically using the Kaplan-Meier method to compare crisis-free survival between treatment groups; the log-rank test was applied to more formally compare time to first crisis between groups. Censoring date was the earlier of the start date of drug tapering and study exit date. The table below summarizes results for these analyses. In Study 10478, the median time to first crisis among patients randomized to Endari treatment was delayed by about 20 days compared to placebo patients; in Study GLUSCC09-01, the delay of median time to first crisis was about 30 days among patients taking Endari compared to placebo. P-values for log-rank tests comparing treatment groups in

Clinical Review

NDA 208587

Endari® (L-glutamine)

each study are considered nominal since this analysis was not pre-specified.

Table 19: Unplanned secondary efficacy endpoint: Time to first sickle cell crisis, by Study and Treatment Group

Endpoint	Study 10478		Study GLUSCC09-01	
	Endari (N = 37)	Placebo (N = 33)	Endari (N = 152)	Placebo (N = 78)
Time to first sickle cell crisis				
Median days to first crisis (95% CI)	64 (15.0, 148.0)	44 (6.0, 86.0)	84 (62.0, 109.0)	54 (31.0, 73.0)
Nominal p-value (log-rank test)	0.5861		0.0152	

SOURCE: Applicant's [Integrated Summary Efficacy Table 22](#)

Time hospitalized was the third unplanned endpoint that was summarized in the Applicant's ISE; the percentage of time hospitalized was defined as the cumulative duration of hospitalization divided by the length of time on study times 100. This endpoint was assessed using an analysis of variance (ANOVA) model with treatment group as the main effect. Results for each study are summarized below.

Table 20: Unplanned secondary efficacy endpoint: Percentage of time hospitalized, by Study and Treatment Group

Endpoint	Study 10478		Study GLUSCC09-01	
	Endari (N = 37)	Placebo (N = 33)	Endari (N = 152)	Placebo (N = 78)
Percentage of time hospitalized				
Least Squares Mean (95% CI)	4.3 (1.23, 7.35)	4.6 (1.34, 7.82)	4.7 (3.51, 5.82)	6.0 (4.41, 7.63)
Median time hospitalized (95% CI)	0 (0, 38)	0 (0, 40)	2.2 (0, 38)	3.6 (0, 56)
Nominal p-value (LS means difference)	0.8982		0.1794	

SOURCE: Applicant's [Integrated Summary Efficacy Table 23](#)

Subgroup Analyses

The Applicant submitted subgroup analyses among a pooled ISE ITT population across both studies in order to increase the number of subjects in each subgroup to make an overall assessment of treatment effect for the primary efficacy endpoint; due to important study differences and issues highlighted earlier in this review, FDA does not consider the pooling of study populations appropriate. The following table summarizes primary efficacy results by subgroups of patients in Study GLUSCC09-01 only; these analyses were performed using the FDA sensitivity analysis population, where incomplete counts for 24 patients are omitted. Using negative binomial regression models with treatment and subgroup main effects, controlling for study site region and baseline hydroxyurea use (unless otherwise specified), with time on study included as an offset and a treatment by subgroup interaction term, estimated rates of sickle cell crises per 48 weeks are presented for each subgroup category by treatment group. Additionally, rate ratios and corresponding 95% confidence intervals compare estimates across treatment groups.

Clinical Review

NDA 208587

Endari® (L-glutamine)

All subgroup analyses should be interpreted with caution since none were pre-specified; these analyses may generate additional hypotheses about the efficacy of Endari among specific subpopulations, but should be considered confirmatory of the primary efficacy result.

Table 21: Efficacy results among subgroups in Study GLUSCC09-01 by treatment group; rate of sickle cell crises per 48 weeks*

	Estimated sickle cell crisis count per 48 weeks (95% CI)		Rate ratio [Endari vs. Placebo] (95% CI)
	Endari (N = 132)	Placebo (N = 74)	
Age group			
≤18	3.3 (2.7, 4.0)	3.5 (3.4, 5.4)	0.95 (0.69, 1.29)
>18	3.6 (2.8, 4.5)	5.5 (4.1, 7.4)	0.67 (0.48, 0.94)
Sex			
Female	3.4 (2.7, 4.2)	3.9 (3.1, 5.0)	0.86 (0.63, 1.17)
Male	3.1 (2.5, 4.0)	4.4 (3.2, 6.0)	0.71 (0.50, 1.02)
Race/Ethnicity			
Black	3.4 (2.9, 4.0)	4.3 (3.6, 5.3)	0.79 (0.62, 1.00)
Hispanic/Other	1.6 (0.4, 6.1)	1.8 (0.5, 6.8)	0.89 (0.28, 2.83)
Hydroxyurea Use at Baseline⁺			
Yes	3.4 (2.8, 4.1)	4.3 (3.4, 5.4)	0.79 (0.59, 1.06)
No	3.2 (2.4, 4.1)	3.8 (2.8, 5.1)	0.83 (0.58, 1.21)
Region of Study Site[^]			
Midwest	4.3 (2.9, 6.6)	4.3 (2.8, 6.6)	1.01 (0.59, 1.73)
Northeast	2.3 (1.7, 3.2)	4.4 (3.1, 6.3)	0.53 (0.33, 0.84)
South Atlantic	3.5 (2.5, 5.0)	2.7 (1.8, 4.1)	1.29 (0.82, 2.05)
South Central	2.9 (2.0, 4.3)	3.9 (2.5, 6.3)	0.74 (0.41, 1.34)
West	3.6 (2.6, 4.8)	4.9 (3.4, 7.1)	0.73 (0.45, 1.17)
Dose Level			
<30 g	3.5 (2.9, 4.3)	3.9 (3.0, 5.1)	0.90 (0.66, 1.22)
30 g	2.9 (2.3, 3.7)	5.0 (4.0, 6.4)	0.58 (0.43, 0.79)

*Based on negative binomial regression model, controlling for study stratification factors

⁺Model controls for region of study site only

[^]Model controls for baseline hydroxyurea use only

SOURCE: FDA Reviewer Analysis

Estimated rates of sickle cell crises per 48 weeks appeared to be similar between treatment groups among pediatric patients; however, among adult patients the magnitude of difference in rates of crises is larger, in favor of Endari (HR: 0.67, 95%CI:[0.48, 0.94]). Because there were no patients of age 65 or older enrolled in the study, it is not possible to assess the treatment effect of Endari among older adults. Treatment dosage was based on body weight, and a similar trend can be observed as with age groups; at the lower dose level, estimated crisis rates were similar between treatment groups, while at the higher dose level the rate of crises per 48 weeks is much lower among Endari patients compared to placebo (HR: 0.58, 95%CI: [0.43, 0.79]). No dose-level or blood-level responses were analyzed in either study. There were no apparent differences in treatment effect by sex. Non-black patients appeared to have experienced lower rates of crises per 48 weeks compared to black patients, irrespective of treatment group; the treatment effect of Endari was similar by race/ethnicity. Among the five regions where study sites were located, patients enrolled at sites in the South Atlantic region and randomized to Endari treatment had a higher average estimate of sickle cell crises per 48 weeks compared to placebo patients at sites in the same region (HR: 1.29, 95% CI: [0.82, 2.05]).

Clinical Review

NDA 208587

Endari® (L-glutamine)

6.4. Statistical Issues

Due to differences in study design and conduct, comparisons of results from Studies 10478 and GLUSCC09-01 are difficult to interpret. Particularly, the primary endpoint – number of sickle cell crises – was defined and classified differently between studies. As a result, patients in Study 10478 experienced a wider range of crises within the 48-week treatment period (0 to 90 crises) compared to patients in Study GLUSCC09-01 (0 to 15 crises). Additionally, early study dropout was high and differential between treatment arms in both studies; more than half of patients enrolled in Study 10478 dropped out of the study before the full 48-week treatment period. For these reasons, the Agency reviewed efficacy results separately for each study. Statistical issues identified from each study are discussed in more detail below.

In Study 10478, there was a high rate of early study withdrawal, with more patients randomized to placebo treatment dropping out early compared to patients randomized to ENDARI treatment. Additionally, data from one of five study sites was omitted due to potential study misconduct; this omission represented more than 10% of patients originally enrolled in the study. This study did not meet its specified significance level in the primary efficacy analysis. Patients were randomized by study site only, and not by baseline hydroxyurea use; this may have led to a heterogeneous study population as rates of hydroxyurea use differed between treatment arms. For these reasons, the efficacy results of Study 10478 do not provide a basis for comparability with Study GLUSCC09-01 results.

In Study GLUSCC09-01, early study withdrawal occurred at a higher rate than expected, and a higher dropout rate occurred among patients randomized to Endari treatment. Additionally, the Applicant specified a method of imputing incomplete sickle cell crisis counts that may have introduced bias in the primary and secondary efficacy results due to differential dropout between treatment arms. As a result, the analytic method specified by the Applicant may not be the optimal method of assessing the primary and secondary efficacy endpoints.

FDA performed sensitivity analyses that made different assumptions about incomplete data on the number of crisis counts experienced through 48 weeks. Additionally, when analytic methods took additional study information into account, such as the time spent on study, results still trended in favor of Endari, but the magnitude of benefit was modest and in some cases, confidence intervals for ratios of rates of sickle cell crises per 48 weeks between treatment groups included a ratio of 1.

These issues were brought before an Oncologic Drugs Advisory Committee in May 2017. The Applicant presented their specified efficacy analyses, as well as several post-hoc sensitivity analyses to assess the robustness of the primary efficacy analysis under different assumptions and analytic methods. The FDA presented statistical issues discussed in this review as well as some reviewer-performed post-hoc exploratory analyses that assessed the impact of different assumptions about incomplete data and analytic methods that accounted for more relevant study information. The committee asked clarifying questions about the Applicant's and FDA's analyses and considered the totality of information presented on the efficacy and safety profile of Endari for the proposed indication.

Clinical Review

NDA 208587

Endari® (L-glutamine)

The committee voted 10 (Yes) to 3 (No) in favor of recommending approval of Endari. Overall, committee members interpreted a modest benefit and low safety risk of Endari over placebo and emphasized a high unmet need for safe and effective treatments for patients with sickle cell disease.

6.5. Conclusions and Recommendations

In summary, there were more early study dropouts than anticipated in Study GLUSCC09-01, with more dropouts from the Endari treatment group. The Applicant used imputation to fill in incomplete sickle cell crisis event counts in Study GLUSCC09-01; due to high and differential dropout rates between treatment groups, the imputation method used by the Applicant may have introduced bias in the primary and secondary efficacy analyses. FDA analyses considered alternative methods of handling incomplete crisis event counts that did not rely on imputation of incomplete counts and incorporated relevant study information such as the time spent on treatment before dropping out of the study. Particularly, a recurrent time-to-event analysis performed by FDA estimated sickle cell crisis rates per 48 weeks of 3 crises for patients treated with Endari vs. 3.8 crises for patients treated with placebo (HR: 0.73, 95%CI: [0.55, 0.99]). Other exploratory analyses performed by FDA and the Applicant yielded results in favor of Endari, though the magnitude of benefit was modest compared to the Applicant's primary efficacy analysis using the CMH test. In the presence of high and differential study dropout, no imputation approach or analytic method is ideal since there is no way to know what the true 48-week crisis counts would have been for patients who dropped out of the study early. This apparent trend of an Endari benefit should be considered in the context of the product's safety profile.

7 Review of Safety

7.1. Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of Endari in this application was based primarily on review of safety data presented in clinical studies GLUSCC09-01 and Study 10478 and are reported herein. Details of the protocol design of both studies were described in Section 5.1.

Additional safety information was sought from the Legacy studies (Studies 8288, 8822, 8775, 10779, and 10511) conducted early in the clinical development program of L-glutamine, and from a review of the published literature.

There was no key safety review issues identified a priori.

7.1.2 Categorization of Adverse Events

In the individual study reports, AEs were coded using differing versions of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events for study 10478 were reported down to the preferred term (PT) and categorized into System Organ Class (SOC) according using MedDRA Version 7.1. Adverse events for Study GLUSCC09-01 were using MedDRA Version 12.0. For the applicants' integrated safety database, all AEs were recoded using MedDRA version 18.0.

Some AE verbatim terms represented a combination of terms, such as 'headache and blurred vision'. In the CSRs, this was handled by only summarizing 1 of the terms. In the integrated summaries, these were split into multiple terms and all terms were summarized.

The following rules were applied specifically to AEs relating to sickle cell pain or crisis: If a term included sickle cell pain or crisis in addition to another sickle cell symptom (such as 'sickle cell back pain'), only the sickle cell pain or crisis was coded. If sickle cell pain was reported along with acute chest syndrome, both terms were coded separately.

Only treatment emergent adverse events (TEAE) were evaluated. Treatment emergent adverse events (TEAE) were defined as any AE with an onset date on or after the date of the first dose of study drug through 30 days after the last dose of study drug. The applicant did not pre-specify any adverse events of special interest.

The parameters of AEs, SAEs, and withdrawals due to AEs were summarized for the demographic subgroups of sex (male or female), age (age group 1: 5 to 12 years, 13 to 18 years, > 18 years, and age group 2: ≤ 18 years or > 18 years), race (black/African American or other), hydroxyurea use at baseline (yes or no), and diagnosis (sickle cell anemia, sickle β⁰-thalassemia, or other including 'sickle cell trait [Hgb SC]' and 'sickle β+-thalassemia').

Clinical Review

NDA 208587

Endari® (L-glutamine)

7.1.3 Pooling of Data.

Seven studies (N= 365 subjects) were conducted by the Applicant as part of the clinical development program for Endari for the treatment of sickle cell disease. See Table of clinical studies in Section 5.1.

Safety data from 298 subjects enrolled in study 10478 and GLUSCC09-01 were included in the pooled integrated safety analyses for this submission.

Data from 5 smaller studies (Study 8288, Study 8822, Study 8775, Study 10779, and Study 10511 – referred to as the LEGACY studies) conducted early in the clinical development program of Endari were not included in the integrated analyses by the Applicant because safety data in these studies were not as explicitly defined as in Study 10478 and Study GLUSCC09-01 (Study 8822 was a dose-finding study and did not collect AE's).

Exposure

The duration of exposure is summarized by treatment group in the table below. The safety population consisted of all subjects enrolled in Study 10478 and Study GLUSCC09-01 who received at least 1 oral dose of Endari or placebo equivalent to 0.3 g/kg administered twice daily, resulting in daily doses of 30, 20, or 10 g based on subject body weight. Of the 298 subjects included in the safety population, 109 (58.3%) subjects received Endari for ≥ 48 weeks (58.3% in the Endari treatment group and 65.8% in the placebo treatment group). A total of 187 subjects received Endari for ≥ 1 day, 136 subjects received Endari for ≥ 6 months (24 weeks), and 109 subjects received Endari for ≥ 48 weeks.

The duration of exposure is summarized by treatment group in the Table below. The number of days of exposure was defined as last day on study medication minus first day on study medication plus 1 (where last day on study medication included the taper phase). Days of exposure were summarized by treatment group using descriptive statistics. The number and percentage of subjects with ≥ 1 day, ≥ 12 weeks, ≥ 24 weeks, ≥ 4 weeks, ≥ 48 weeks of exposure are provided, as well as the total number subject-years of exposure computed as the number of subject-days divided by 365.25.

Table 22: Summary of Drug Exposure (Safety Population)

	Endari N = 187	Placebo N = 111	Total N = 298
Duration of exposure* (days) Mean (SD)	268.9 (126.92)	283.3 (121.63)	274.3 (124.96)
Subjects with exposure, n (%)			
≥ 1 day	187 (100.0)		
≥ 12 weeks	161 (86.1)	98 (88.3)	259 (86.9)
≥ 24 weeks	136 (72.7)	89 (80.2)	225 (75.5)
≥ 48 weeks	109 (58.3)	73 (65.8)	182 (61.1)
Number of subject-years**	137.7	86.1	223.8

FDA generated table

Data Source: Applicants ISS Table 3

Clinical Review

NDA 208587

Endari® (L-glutamine)

7.2. Adequacy of Safety Assessments

7.2.1 Safety Population

The safety population consisted of 298 subjects (187 subjects treated with Endari and 111 subjects treated with placebo) who received at least 1 oral dose of Endari or placebo equivalent to 0.3 g/kg administered twice daily, resulting in daily doses of 30, 20, or 10 g based on subject body weight. Demographics and baseline characteristics of patients in the safety population are shown in the table below.

The majorities of subjects in both treatment groups were black or African American (97.3% in the Endari treatment group and 96.4% in the placebo treatment group) and were 18 years of age or older (57.2% in the Endari group and 56.8% in the placebo group). Ninety percent of subjects in the overall safety population had a diagnosis of sickle cell anemia and 63.4% were being treated with HU at baseline (66.3% in the Endari treatment group and 58.6% in the placebo treatment group). In Study 10478, the mean number of SCCs in the year prior to screening was 9.8 in the Endari and 8.8 in the placebo treatment group. In Study GLUSCC09-01, the mean number of SCCs in the year prior to screening was 3.9 in the Endari and 4.1 in the placebo treatment group.

Table 23: Demographics, Safety Population (Study 10478 and GLUSCC0901)

	Endari N = 187 n (%)	Placebo N = 111 n (%)	Total N = 298 n (%)
Age (years)			
median	22.0	21.0	22.0
Range (min, max)	(5, 58)	(5, 58)	(5, 58)
Age group, n(%)			
5-12	35 (18.7)	19 (17.1)	54 (18.1)
13-18	45 (24.1)	29 (26.1)	74 (24.8)
>18	107 (57.2)	63 (56.8)	170 (57.0)
Sex, n (%)			
Male	170 (57.0)	53 (47.7)	137 (46.0)
female	103 (55.1)	58 (52.3)	161 (54.0)
Race			
Black	182 (97.3)	107 (96.4)	289 (97.0)
Other	5 (2.7)	4 (3.6)	9 (3.0)
Diagnosis			
Sickle cell anemia	169 (90.4)	99 (89.2)	268 (89.9)
Sickle β^0 -thalassemia	16 (8.6)	12 (10.8)	28 (9.4)
Other ¹	2 (1.1)	0	2 (0.7)
Hydroxyurea use at baseline, n (%)			
Yes	124 (66.3)	65 (58.6)	189 (63.4)
No	63 (33.7)	46 (41.4)	109 (36.6)

¹ Sickle β^+ -thalassemia or sickle cell trait (Hgb SC)

Studies included: Study 10478 and Study GLUSCC09-01.

Source: FDA analysis

Reviewer comment: The safety population included both pediatric and adult patients. In response to an information request, the Applicant indicated that children less than 5 years of

Clinical Review

NDA 208587

Endari® (L-glutamine)

age were excluded from enrollment in Study 10478 and Study GLUSCC09-01 due to the major difference in clinical manifestations seen in the complications of sickle cell disease compared to patients 5 years of age and older. This reviewer agrees with the Applicants assessment that including children less than 5 years of age was not feasible because it would have required a different set of end points. The racial/ethnic composition of the safety population is reflective of the population of patients with Sickle cell anemia in the general population. Use of the anti-sickling agent HU was permitted in both studies. The higher proportion of patients in the Endari treatment group using HU at baseline is because randomization was not stratified by HU use in Study 10478.

7.2.2 Explorations for Dose Toxicity Relationship

All subjects received an oral dose of Endari or placebo equivalent to 0.3 g/kg administered twice daily, resulting in daily doses of 30, 20, or 10 g based on subject body weight. The Applicant did not provide summaries of exposure by dose. Since Endari dosing was weight based, FDA explored the occurrence of toxicities or adverse events in the safety population by body weight. These results are reported in section 7.5.3 below.

7.2.3 Special Animal and/or In Vitro Testing

There is no new nonclinical information about Endari in this submission that warrants special clinical testing.

7.2.4 Routine Clinical Testing

The schedule of safety evaluations for each protocol was described in Section 5.3.

7.2.5 Metabolic, Clearance, and Interaction Workup

The results of the studies of human pharmacokinetics and pharmacodynamics relevant to safety were summarized in Section 4.3

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

L-Glutamine is the most abundant free amino acid found in the body (Watford 2008). L-glutamine is widely available as a dietary supplement for bodybuilding. There are no known safety concerns associated with glutamine supplementation.

Adverse effects of amino acid supplementation may be a consequence of elevation of the concentration of the amino acid or its metabolic product in the blood or in target tissues (Garlick 2001). Glutamine degradation yields glutamate and ammonia. Plasma glutamine or ammonia concentrations were not measured in Studies 10478 and GLUSCC09-01. A review of the published literature by FDA did not reveal reports of increased ammonia or glutamate levels in subjects who received high intakes of glutamine (Ziegler, Benfell et al. 1990).

Some researchers have suggested that amino acid supplement could also cause alterations of metabolism (Garlick 2001). Daily oral supplementation with glutamine (with or without sitagliptin) has been associated with decreased glycaemia in well-controlled type 2 diabetes patients in some clinical studies (Samocho-Bonet, Chisholm et al. 2014). In the safety population for this Application, hypoglycemia was reported as a TEAE in less than 1% of Endari treated patients.

Electrolyte disturbances (such as hyponatremia resulting from glycine administration (Santosham, Burns et al. 1986); hyperkalemia from arginine hydrochloride consumption (Massara, Cagliero et al. 1981)) have been reported following single amino-acid supplementation. Glutamine supplementation was not associated with electrolyte disturbances in the safety population for this Application. Hypokalemia, hypomagnesemia, hyperkalemia and hypophosphatemia occurred in less than 5% of Endari treated patients and occurred at a comparable rate between Endari and placebo treated patients.

7.3. Major Safety Results

7.3.1. Deaths

Four deaths occurred in safety population. Three deaths occurred in Study GLUSCC09-01. One death occurred in Study 10478. All 4 deaths occurred in Endari-treated subjects. Three deaths were treatment emergent. One death occurred more than 30 days (120 days) after the last dose of study medication and was not considered treatment emergent. None of the 3 treatment emergent deaths were considered to be related to study drug by the investigator.

The crude mortality rate for subjects in the Endari treatment group was 1.6% and the exposure-adjusted mortality rate was 2.2 deaths per 100 subject-years. No deaths occurred in the placebo treatment group. A summary of mortality by treatment group is presented in Table 6 below.

Table 24: Summary of Mortality, by treatment group, (Safety Population)

Table 6. Summary of Mortality, by Treatment Group (Safety Population)

Parameter	L-glutamine N = 187	Placebo N = 111
Number of treatment-emergent deaths	3	0
Crude mortality (%)	1.6	0.0
Total exposure in subject-years	137.7	86.1
Mortality per 100 subject-years	2.2	0.0

Source: Applicant's ISS

Summary of treatment- emergent deaths

Below is a summary of the 3 treatment- emergent death cases.

Case 1: Patient 02-504 was a 46 year old African-American female with a history of sickle cell anemia previously treated with oral HU 1500mg daily from June 1993. She had two sickle-cell crises in the year prior to enrollment. She was enrolled in Study GIUSCC09-01 and was treated with Endari 15g PO twice daily.

After approximately 41 weeks of treatment, she presented to the emergency room “due to acute sickle cell crisis” with CPR in progress on arrival at the ER. Cardiopulmonary resuscitation (CPR) was unsuccessful and the patient was pronounced dead within 30 minutes of arrival. This unspecified SAE was reported as sudden death, severe in intensity and not related to study drug. The cause of death was listed as cardiopulmonary arrest. The family declined an autopsy. A Medwatch form for this death was submitted to the FDA.

Clinical Review

NDA 208587

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While on study, Patient 02-504 was compliant and completed all required study visits for 40 weeks. During this time, this patient had a single episode of vaso-occlusive crisis 1. This SAE was treated successfully with concomitant medications and considered un-related to study drug by the investigator. No other significant abnormal findings on physical exams or laboratory results were reported for this patient.

Review Comment: The exact cause of death of this patient cannot be determined in the absence of an autopsy report. The Medwatch form did not provide additional information. FDA requested the death report of this patient from the Applicant however this was not available. In the absence of an autopsy report, the causal association between Endari treatment and death in this patient cannot be assessed by this reviewer.

Case 2: **Patient 02-516** was a 45-year-old African-American male with sickle-cell anemia who was enrolled in Study GIUSCC09-01. He was treated with oral Endari 10g twice daily and participated in the study for 349 days.

While on study, the following SAEs of special interest were reported for this patient:

- Acute infarct/ TIA, moderate in severity, treated with concomitant medications, and resolved with sequelae, not likely related to study drug.
- Acute/chronic renal failure (with hospitalization), severe in intensity, treated with concomitant medications, and resolved completely. Not related to study drug.
- Cardiac arrest

Other SAEs reported for this patient while on study were - slurred speech, abdominal vaso-occlusive crisis (2 episodes).

He died on Study Day 349 from cardiac arrest. No further information was provided. This event was assessed by the investigators as severe in intensity, resulting in fatality, but not related to study drug. A Medwatch form was not submitted to the IND when this event was reported because the event was considered unrelated to study drug.

Review Comment: The information provided is inadequate to determine the cause of death in this patient. The circumstances of his death are unknown. FDA requested the death report of this patient from the Applicant however this was not provided. A possible role of Endari treatment in causing the cardiac arrest event cannot be determined by this reviewer.

Case 3: Patient 101-014 was a 37-year-old woman with sickle cell anemia and a history of avascular necrosis of both hips, acute renal failure, aplastic crisis, hemochromatosis, hepatic insufficiency, intermittent seizures, pulmonary hypertension, ankle edema, mild icterus, right toe numbness, systolic murmur, and bilateral edema of the lower extremities. She had been previously treated with hydroxyurea (last dose of HU was 10 years prior to enrollment) and had 3 episodes of crises and 3 hospitalizations in the year prior to enrollment. She was enrolled in Study 10478 and was treated with Endari 15g PO twice daily. She was hospitalized with altered consciousness and hypoglycemia on Study day 331 after 2 days of abdominal pain. She was treated with 50% dextrose and Narcan (naloxone) and was transfused with blood and fresh frozen plasma. She died on Study day 331 after unsuccessful CPR at the ER.

Clinical Review

NDA 208587

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Her cause of death listed on her death summary report was 1) Respiratory failure, status-post cardiopulmonary arrest; 2) sickle cell crisis; 3) severe anemia; 4) severe hypoglycemia; 5) liver cirrhosis and 6) renal failure likely secondary to liver failure and hepato-renal syndrome; 7) history of right total hip replacement; 8) history of cholecystectomy and 9) Hypercoagulopathy secondary to liver cirrhosis and End Stage Liver Disease. The investigator considered the altered consciousness and hypoglycemia to be severe and unrelated to the study drug. A Medwatch form was not submitted to the IND when this event was reported because the event was considered unrelated to study drug.

Review Comment: The information provided is inadequate to determine the cause of death in this patient. The death report for this patient was requested from the sponsor, but this was not available. A possible role of Endari treatment in causing the events of altered consciousness and hypoglycemia cannot be determined out by this reviewer.

Summary of non-treatment emergent death

Patient 14-512 was a 10-year-old African-American boy with sickle-cell anemia and a medical history of cholecystectomy, reactive airway disease, delayed hemolytic reaction, iron overload, overweight, icterus, pallor, and a limping gait. He was enrolled in Study GIUSCC09-01 and treated with oral Endari 10g twice daily. He completed 48 weeks of treatment, 2 weeks of tapering successfully completed follow-up.

While on study, the following serious adverse events were reported for this patient:

- Acute Sickle-Cell Pain Crisis
- Hematuria

Three months after exiting the study, he was hospitalized with pain crisis. The following day, he became worse and was admitted to the Pediatric Intensive Care Unit (PICU). His condition deteriorated and he died on the same day at the PICU. His immediate cause of death was reported by the investigators as due to “cardiopulmonary arrest secondary to SIRS, DIC, septic shock, questionable acute abdomen, and HbSS. This SAE was assessed by investigators as not related to study drug.

Review Comment: I agree with the Applicant that this non-treatment emergent adverse event in this patient is unlikely to be related to study drug. The event also occurred more than 3 months after discontinuation of study treatment and is therefore unlikely to be due to drug withdrawal.

Additional information on Mortality rates

At the request of FDA, the Applicant provided evidence to show that the mortality rate observed in patients treated with Endari in the safety population is comparable to the expected mortality rate in the Sickle cell patients. The Applicant compared the mortality rate observed in the Endari safety population to safety data from 2 studies (Steinberg et al 2003 and Ataga et al 2017) that also enrolled patients with a history of 2 or more sickle cell crises per year. Steinberg et al evaluated the effect of Hydroxyurea on mortality and morbidity in adult sickle cell anemia patients using data from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) trial with 9 years of follow-up. In this study, the number of deaths per 100 patient-years was 3.1 for patients originally randomized to hydroxyurea, 3.6 for patients originally randomized to placebo, and 3.3 for the overall population. The Applicant stated that these rates are all higher

Clinical Review

NDA 208587

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than the mortality rate per 100 patient-years seen in the Endari safety population and thus provides evidence that the mortality rate observed in the Endari population is not greater than the expected mortality rate in this population.

A second paper (Ataga, Kutlar et al. 2017) describes a one year study with a similar patient population as our safety population in terms of inclusion criteria such as, age, HU use, and disease severity; this paper analyzed the use of a P-selectin inhibitor (crizanlizumab) to reduce sickle cell crisis. Of the 65 patients in the placebo group of this study, 2 patients died, thus the crude mortality rate was 3.08%. The minimum mortality rate per 100 patient-years can be estimated by assuming that each patient had exposure equal to 1 year (the length of the study), i.e. 65 patient-years of exposure and a mortality rate of 3.08 per 100 patient-years. Note that this is an over-estimate of exposure since 24 patients withdrew early. The Applicant concluded that both the crude mortality rate and the rate per 100 patient-years in this study are higher than the mortality rates observed in the Endari safety population.

Review Comment: The mortality rate per 100 patient-years and the crude mortality rate observed with Endari in the overall safety population were 2.2 and 1.6% respectively. The role of Endari treatment in causing these fatal SAE cannot be categorically ruled out by this reviewer but does not seem likely for the following reasons:

L-Glutamine is an essential amino acid used as a nutritional supplement and marketed drug (NutreStore®) for the treatment of short bowel syndrome (SBS) in patients receiving specialized nutritional support (used in conjunction with a recombinant human growth hormone). There have been no deaths or safety reports associated with NutreStore®. However, it should be noted that NutreStore® is administered for a maximum of 16 weeks whereas Endari for the SCD indication will be administered chronically and possibly for a lifetime.

The Applicant compared the mortality rate observed in the Endari safety population to safety data from 2 studies (Steinberg et al 2003 and Ataga et al 2017) that evaluated other treatments for a similar group of patients with SC and concluded that the mortality rates observed in these studies were all higher than the rates observed in the Endari safety population.

Steinberg et al reported findings from an observational follow-up study of mortality in patients (n=299) with Sickle cell Anemia (SCA) who originally participated in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), conducted in 1992-1995, to determine if hydroxyurea reduces vase-occlusive events. Follow-up data through May 2001 were complete for 233 patients. In this study, the number of deaths per 100 patient-years was 3.1 for patients originally randomized to hydroxyurea, 3.6 for patients originally randomized to placebo, and 3.3 for the overall population. HU treatment was associated with a 40% reduction in mortality (p=0.04) compared to placebo after 9 years of follow up.

Patients enrolled in the MSH trial were however, required to have a history of 3 or more painful crises episodes in the 12 months prior to enrollment and may have been a more high risk population compared to those enrolled in the Endari pivotal trial. The MSH trial, results also must be interpreted with caution because in the follow up period (1996-2001), HU use was no longer randomized and patients could continue, stop, or start hydroxyurea so improvements in mortality outcomes may be due to other factors outside HU use. A more appropriate comparison for the

Clinical Review

NDA 208587

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purposes of this NDA will be a comparison of the mortality rates during the MSH randomized trial to mortality outcomes in the Endari safety population. Eight patients died during the two year randomized MSH trial (2 receiving HU and 6 receiving placebo). This corresponds to a crude mortality rate of 1.3 and deaths per 100 person-years of 3.1 in the HU treatment group. For the placebo group, the crude mortality rate and deaths per 100-person years were 4.1 and 3.6 respectively.

Ataga et al conducted a double-blind, randomized, placebo-controlled, phase 2 trial to evaluate the safety and efficacy of crizanlizumab, an antibody against the adhesion molecule P-selectin, in patients with sickle cell disease(n=198). Patients enrolled in this study had a similar risk profile (at least 2 crises in the 12 months prior to enrollment) compared to those enrolled in the Endari studies and were treated with crizanlizumab or placebo over a 52 week treatment period. A total of 5 patients died during the trial, including 3 patients treated with crizanlizumab and 2/65 patients in the placebo group corresponding to a crude mortality rate of 3.08 and an estimated mortality rate per 100 patient-years of 3.08 both of which are higher than the rate observed in the Endari safety population.

SCD is associated with an overall decreased life expectancy. The mortality rate observed in patients treated with Endari in the safety population was not greater than the observed mortality rates in other clinical studies of patients with SCD.

7.3.2. Nonfatal Serious Adverse Events

This section provides a summary of non-fatal Serious Adverse Events (SAE) that occurred in all patients who received at least 1 dose of Endari from all studies included in the integrated safety database. Safety data from 4 other smaller exploratory studies (Study 8288, Study 8775, Study 10779 and Study 10511) are presented separately.

At least one treatment-emergent SAE occurred in 141 subjects (75.4%) in the Endari treatment group and 89 subjects (80.2%) in the placebo treatment group. The most common SAEs occurring the in the Endari group were sickle cell crisis (66.3%), acute chest syndrome (7.0%), and pneumonia (4.8%). The table below shows the numbers and percentages of subjects with SAEs by System Organ Class in both study arms.

Table 25: SAEs occurring in $\geq 2\%$ of Endari-treated Subjects, by SOC (Safety Population)

SOC	Endari N = 187		Placebo N = 111	
	Number of subjects	(%)	Number of subjects	(%)
Blood and lymphatic system disorders	127	67.9	80	72.1
Respiratory, thoracic and mediastinal disorders	19	10.2	28	25.2
Infections and infestations	18	9.6	19	17.1
General disorders and administration site conditions	16	8.6	8	7.2
Gastrointestinal disorders	10	5.4	5	4.5
Musculoskeletal and connective tissue disorders	5	2.7	6	5.4

Clinical Review

NDA 208587

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Nervous system disorders	5	2.7	1	0.9
Pregnancy, puerperium and perinatal conditions	4	2.1	3	2.7

Source: FDA analysis

The table below shows SAEs which occurred in at least 2% of subjects in the Endari treatment group, by PT. The most common SAEs occurring in the Endari group were sickle cell crisis (66.3%), acute chest syndrome (7.0%), and pneumonia (4.8%).

Table 26: SAEs occurring in $\geq 2\%$ of Endari-treated Subjects, by PT (Safety Population)

PT	Endari (N = 187)		Placebo (N = 111)	
	Number of subjects	(%)	Number of subjects	(%)
Sickle cell anemia with crisis	124	66.3	80	72.1
Acute chest syndrome	13	6.9	21	18.9
Pneumonia	9	4.8	10	9.0
Chest pain	5	2.7	2	1.8
Pyrexia	5	2.7	4	3.6
Asthma	4	2.1	3	2.7
Pregnancy	4	2.1	3	2.7

Source: FDA Reviewer analysis

Majority of these SAEs were considered unrelated to Endari treatment by the Applicant: In both the Endari and placebo treatment groups, 3 subjects had at least 1 SAE considered related to study drug by the investigator (1.6% Endari, 2.7% placebo). In the Endari group, SAEs considered by the investigator to be related to study drug included hypersplenism (n=1), sickle cell anemia with crisis (n=1), abdominal pain (n=1), and chest pain (n=1).

Narratives of nonfatal related serious adverse events

Case 1: Patient 0901-21-101 was a 10-year-old Black female patient with sickle cell anemia and no history of treatment with hydroxyurea or any other anti-sickling medication. Her medical history included right port-A-cath placement, constipation, headache, and gastroesophageal reflux disorder. She was enrolled in Study GLUSCC0901 and was treated with Endari.

On Study Day 234, she visited a clinic for moderate left upper quadrant abdominal pain which was deemed to be due to her chronic constipation. Five days later, her abdominal pain worsened. She was seen in the emergency room where an abdominal ultrasound examination showed increased splenomegaly. She was diagnosed with moderate hypersplenism and was hospitalized due to these events. The abdominal pain resolved 19 days after the last dose of Endari and the patient was discharged from the hospital. The investigator assessed the abdominal pain and hypersplenism as possibly related to Endari.

Concomitant medications at the time of the abdominal pain and hypersplenism included folic acid, ibuprofen, deferasirox, ranitidine, ascorbic acid, tocopherol acetate, paracetamol, macrogol and docusate sodium.

Clinical Review

NDA 208587

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Treatment with Endari was discontinued on Study Day 234 due to hypersplenism. Twenty-one days after the last dose of Endari, the patient was discontinued from the study due to the event of hypersplenism.

Review Comment: This reviewer agrees that the occurrence of hypersplenism in this patient is serious. However, considering the long treatment duration (234 days), it is unlikely that these events were due to Endari treatment. The use of several concomitant medications also confounds evaluation of the association between Endari and hypersplenism in this patient.

Case 2: Patient 0901-08-503 was a 37-year-old Black male patient with sickle cell anemia treated with hydroxyurea since 2008. His relevant medical history included flow murmur, priapism and acute chest syndrome. He was enrolled in Study GLUSCC09-01 and treated with Endari from February 3, 2011. One hour after taking Endari on study day 1, he experienced severe chest pain (extended to the upper back and shoulders), moderate dyspnea, and a frontal headache. Treatment with Endari was discontinued on the same day due to these events. His symptoms improved with pain medications - oxycodone and methadone. The next day, physical examination was unremarkable except with Grade II/VI heart murmur and diminished strength in his left leg. An ECG showed normal sinus rhythm, nonspecific T wave abnormality and with no significant changes from his baseline EKG.

Laboratory tests showed decreased blood counts, but his baseline counts were not provided. One day later, the chest pain and dyspnea resolved. The investigator considered the event of chest pain to be medically significant. The investigator assessed the chest pain as possibly related to Endari.

Concomitant medications at the time of the chest pain included folic acid, ibuprofen, methadone, oxycodone, hydroxycarbamide, bicalutamide, ranitidine, Senna, pantoprazole, docusate sodium and oxycodone hydrochloride. One day after the only dose of Endari, the patient was discontinued from the study due to withdrawal of consent.

Review Comment: This reviewer agrees with the investigators assessment that the event of chest pain was medically significant however; it is unlikely that Endari caused chest pain in this patient due to the short time interval (one hour) between study drug administration and the onset of symptoms in this patient. Moderate dyspnea may have been due to anxiety.

Case 3: Patient 102-005 was a 13-year-old Black male patient with sickle cell anemia, treated with hydroxyurea and a medical history including priapism, murmur and attention deficit hyperactivity disorder (ADHD). He was enrolled in Study 10478 on the Endari treatment arm. On Study Day 166, he was hospitalized for left knee pain which had started 2 days prior. On Study Day 167, he was diagnosed with moderate sickle cell anemia with crisis. He was treated with narcotics, antibiotics and I unit of packed red blood cells during this hospitalization. Endari was not discontinued. On Study Day 171, he an abdominal ultrasound was consistent with splenic sequestration. On Study Day 176, the sickle cell crisis episode resolved without sequelae and he was discharged from the hospital on the same day. The patient received his last dose of Endari on Study Day 344 and completed the study on Study Day 378. The investigator assessed the sickle cell anemia with crisis as possibly related to Endari.

Clinical Review

NDA 208587

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Concomitant medications at the time of the sickle cell anemia with crisis included hydroxyurea, dexemethylphenidate, ibuprofen; diphenhydramine; docusate sodium; amotidine; loratadine; macrogol; Senna alexandrina; and lansoprazole.

Review Comment: Sickle cell anemia with crises is common in patients with SCD. This reviewer agrees that the occurrence of hypersplenism in this patient is serious. However, considering the long treatment duration (171 days), it is unlikely that these events were due to Endari treatment. The concomitant use of other medications also confounds evaluation of the association between Endari and hypersplenism in this patient.

Overall, 2 SAEs of hypersplenism were reported in Endari treated patients in the safety population. Both cases of hypersplenism occurred in pediatric subjects. This is not surprising since splenic sequestration occurs much more commonly among in pediatric compared to adult patients with sickle cell disease. No cases of hypersplenism occurred in placebo treated patients however, randomization to Endari versus placebo was in a 2: ratio. A role of Endari treatment in causing the events of hypersplenism appears unlikely.

7.3.3. Dropouts and/or Discontinuations

This section provides a summary of dropouts and/or discontinuations that occurred among all subjects in the safety population (Studies GLUSCC09-01 and Study 10478).

Overall, 115/187 (61.5%) subjects in the Endari treatment group and 71/111 (64.0%) subjects in the placebo treatment group completed the study. The most common reason for discontinuation in both treatment groups was consent withdrawn (26 subjects [13.9%] in the Endari treatment group and 14 subjects [12.6%] in the placebo treatment group).

Table 27: Disposition of Subjects, Safety Population

Parameter	Endari n = 187 n (%)	Placebo n = 111 n (%)	Total N = 298 N (%)
Completed study	115 (61.5)	71 (64.0)	186 (62.4)
Discontinued study prior to Week 48	72 (38.5)	40 (36.0)	112 (37.6)
Reasons for discontinuation			
Consent withdrawn	26 (13.9)	14 (12.6)	40 (13.4)
Noncompliance	17 (9.1)	10 (9.0)	27 (9.1)
Lost to follow-up	6 (3.2)	4 (3.6)	10 (3.4)
AEs	5 (2.7)	1 (0.9)	6 (2.0)
Death	3 (1.6)	0	3 (1.0)
Other	15 (8.0)	11 (9.9)	26 (8.7)

Studies included: Study 10478 and Study GLUSCC09-01.

Source: FDA Reviewer Analysis

Reviewer comment: Overall, in the safety population, the study discontinuation rate was slightly higher among Endari treated patients than among those treated with placebo however, reasons for discontinuation were similar between treatment groups. Few patients in both treatment groups were lost to follow up.

Clinical Review

NDA 208587

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Most discontinuations in both study arms were due to withdrawal of consent however, these discontinuations did not appear to be related to the occurrence of adverse events. A review of the narratives for patients who withdrew consent revealed a variety of reasons with no particular trend such as – relocation, social issues, “taking too many medication”, inability to tolerate powder formulation (bitter), withdrawal of consent by parents/family, fear of interaction with other medications and feeling worse. A review of the verbatim text for subjects treated with Endari who discontinued due to ‘other’ reasons also revealed a variety of reasons including pregnancy, relocation to another state, initiating chronic transfusions or bone marrow transplant, initiation of alternative anti-sickling agent and ineligibility for study. Among placebo treated subjects, ‘other’ reasons for discontinuations included lack of efficacy, ineligibility for study, pregnancy, relocation and initiating chronic transfusions or bone marrow transplant.

7.3.4. Significant Adverse Events

Treatment Emergent Adverse Events (TEAEs) That Led to Withdrawal

The table below shows the proportion of patients with TEAEs leading to study drug withdrawal in the Endari and placebo treated patients in the safety population. The proportion of TEAEs leading to withdrawal was higher in the Endari treated group (2.7%, 5 subjects) compared to the placebo treatment group (0.9%, 1 subject).

In the Endari treatment group, 3 subjects (1.6%) had at least 1 TEAE leading to withdrawal that was considered to be related to study drug by the investigator; no subjects in the placebo treatment group had drug-related TEAEs that led to withdrawal. The drug-related TEAEs that led to withdrawal in the Endari treatment group were hypersplenism, abdominal pain, dyspepsia, and hot flush (1 subject each [0.5%]). Of the 5 Endari treated patients who had study drug withdrawn due to a TEAE, 2 patients were using hydroxyurea at baseline (not shown in table).

Table 28: TEAEs leading to study drug withdrawal, Safety Population (N=298)

	Endari N = 187 n (%)	Placebo N = 111 n (%)
Subjects with ≥ 1 TEAE that led to study withdrawal	5 (2.7)	1 (0.9)
Hypersplenism*	1(0.5)	0 (0.0)
Abdominal pain*	1(0.5)	0(0.0)
Dyspepsia*	1(0.5)	0(0.0)
Burning sensation	1(0.5)	0(0.0)
Pregnancy	1(0.5)	1 (0.9)
Hot flash*	1(0.5)	0

*Drug related TEAEs
FDA generated table

Review Comment: *Although the proportion of patients with TEAEs leading to study drug withdrawal was slightly higher in the Endari compared to the placebo treated patients; the difference was minimal (2.7 vs 0.9%). In 2 patients, treatment was withdrawn as a precautionary measure due to pregnancy. The occurrence of TEAEs leading to withdrawal does not appear to be*

Clinical Review

NDA 208587

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related to HU use because of greater proportion of subjects with related TEAEs leading to withdrawal did not use HU at baseline.

7.4. Supportive Safety Results

7.4.1. Common Adverse Events

This section provides a summary of common adverse events reported by the Applicant for all subjects in the combined safety population (GLUSCC09-01 and study 10478) and separately for subjects enrolled in the 4 legacy studies with AE data.

TEAEs occurring in $\geq 5\%$ of Endari-treated subjects by decreasing frequency of PT are shown in the table below. The majority of patients in the Endari treatment group (180 subjects [96.3%]) and in the placebo treatment group (108 subjects [97.3%]) reported at least 1 TEAE. The 3 most commonly reported TEAEs, in the Endari treated patient group, were sickle cell anemia with crisis (152 subjects [81.3%] in the Endari treatment group and 97 subjects [87.4%] in the placebo treatment group), constipation (40 subjects [21.4%] in the Endari treatment group and 20 subjects [18.0%] in the placebo treatment group) and nausea (36 subjects [19.3%] in the Endari treatment group and 16 subjects [14.4%] in the placebo treatment group).

Constipation and nausea occurred slightly more commonly among patients treated with Endari than among placebo treated patients (constipation 21.4% versus 18.0% and Nausea 19.3% vs 14.4% in Endari versus placebo treated patients respectively) and unlikely to be clinically significant. Pyrexia and acute chest syndrome occurred more frequently in placebo treated patients (pyrexia 17.1% versus 27.9% and acute chest syndrome 10.2% vs 21.6% in Endari versus placebo treated patients respectively). For all other TEAEs, the proportions of subjects reporting events were similar in both treatment groups.

Table 29: TEAEs occurring in $\geq 10\%$ of Endari-treated Subjects, by PT (Safety Population)

PT	Endari N = 187		Placebo N = 111	
	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Sickle cell anemia with crisis	154	82.4	97	87.4
Constipation	40	21.4	20	18.0
Nausea	36	19.3	16	14.4
Headache	35	18.7	17	15.3
Pyrexia	32	17.1	31	27.9
Cough	29	15.5	15	13.5
Upper respiratory tract infection	26	13.9	20	18.1
Pain in extremity	25	13.4	8	7.2
Vomiting	24	12.8	14	12.6
Back pain	23	12.3	6	5.4
Chest pain	23	12.3	10	9.0
Arthralgia	22	11.8	15	13.5
Abdominal pain	19	10.2	10	9.0
Abdominal pain upper	19	10.2	8	7.2

Clinical Review

NDA 208587

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Acute chest syndrome	19	10.2	24	21.6
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Studies included: Study 10478 and Study GLUSCC09-01.

AEs are counted only once per subject within the MedDRA category

Legacy studies

In Study 8288 {Niihara, 1998 #33, 3 out of 7 patients enrolled experienced at least one AE. The most commonly reported AE was constipation (2 subjects [28.6%]) and hypertension (2 subjects [28.6%]).

In Study 10779, 9 out of 14 patients enrolled (64.3%) experienced at least one TEAE; the most commonly reported TEAEs were sickle cell anemia with crisis (4 subjects [28.6%]) and upper abdominal pain (2 subjects [14.3%]).

In Study 8775, all patients treated with L-glutamine (17 subjects [100%]) and 14/15 patients treated with placebo (93.3) experienced at least one TEAE. The most commonly reported TEAEs were sickle cell anemia with crisis (L-glutamine: 8 subjects [47.1%], placebo: 10 subjects [66.7%]) and constipation (L-glutamine: 8 subjects [47.1%], placebo: 10 subjects [66.7%]).

In Study 10511 4/5 patients treated with L-glutamine (80.0%) and 7/10 patients treated with placebo (70.0%) experienced at least one TEAE. The most commonly reported TEAEs were sickle cell anemia with crisis (L-glutamine: 1 subject [20.0%], placebo: 4 subjects [40.0%]).

TEAEs related to study treatment

The table below shows TEAE considered by the investigator to be possibly, probably or definitely related to study treatment in the safety population. Drug related TEAEs occurred in 35 subjects (18.7%) in the Endari group and 15 subjects (13.5%) in the placebo group. Constipation was the most common TEAE considered possibly, probably or definitely related to Endari treatment.

Table 30: Related TEAEs occurring in ≥ 1% of Endari-treated Subjects, by PT (Safety Population)

PT	Endari N = 187		Placebo N = 111	
	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Subjects with ≥1 drug-related TEAE	35	18.7	15	13.5
Constipation	14	7.5	5	4.5
Abdominal pain upper	5	2.7	1	0.9
Nausea	5	2.7	1	0.9
Abdominal pain	4	2.1	4	3.6
diarrhea	3	1.6	1	0.9
Vomiting	3	1.6	3	2.7
Hypersplenism	2	1.1	0	0.0
Increased appetite	2	1.1	0	0.0
Pruritus	2	1.1	1	0.9
Sickle cell anemia with crisis	2	1.1	1	0.9

Source: FDA Reviewer Analysis

Clinical Review

NDA 208587

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Review Comment: The frequency of common adverse events and frequency of drug related adverse events in the Endari and placebo treatment groups are comparable. Safety findings from the Legacy studies are consistent with the efficacy findings in the Safety population

7.4.1 Laboratory Findings

This section provides a summary of changes in hematological and non –hematological laboratory parameters in the safety population (Study 10478 and GLUSCC0901) reported by the Applicant and confirmed by FDA analysis.

Hematological parameters

The Applicant evaluated changes from baseline to end of treatment for the hematology parameters of RBC, hemoglobin, hematocrit, reticulocytes (count), and reticulocytes /erythrocytes (percent). See table below.

At baseline, mean (SD) hematocrit values were similar between the Endari [26 (7.5%)] and placebo groups [25 (8.2%)]. RBC count at baseline was also similar between the 2 treatment groups with mean (SD) of 2.80 (0.647) x 10¹²/L and 2.86 (0.570) x 10¹²/L, respectively. There was little change from baseline to the end of treatment for HCT and RBC for both treatment groups. Similarly, at baseline, the mean reticulocyte count and reticulocyte/erythrocyte percentage were similar between the Endari and placebo groups; and the mean changes from baseline to the end of treatment were similar between the two groups.

At baseline, mean hemoglobin was slightly lower in the Endari group (131.95 [187.477] g/L) compared with the placebo group (151.82 [220.430] g/L). The mean (SD) change from baseline to the end of treatment was -13.61 (95.376) g/L in the Endari group and -24.14 (145.731) g/L in the placebo group, so at the end of the treatment period, mean hemoglobin levels were comparable between the two groups.

Table 31: Time Point Value and Change From Baseline in Hematology Parameters, Safety Population (N=298)

Clinical Review
NDA 208587
Endari® (L-glutamine)

Parameter	L-glutamine N = 187		Placebo N = 111	
	Time Point Value	Change from Baseline	Time Point Value	Change from Baseline
RBC (x 10¹²/L)				
Baseline				
n	187		111	
Mean (SD)	2.80 (0.647)		2.86 (0.570)	
Median	2.66		2.80	
Min, max	1.7, 5.0		1.7, 4.7	
End of treatment ^a				
n	180	180	107	107
Mean (SD)	2.79 (0.649)	-0.01 (0.363)	2.90 (0.642)	0.04 (0.410)
Median	2.70	-0.03	2.82	0.00
Min, max	1.6, 5.2	-1.2, 1.8	1.8, 4.8	-0.8, 1.6
Hemoglobin (g/L)				
Baseline				
n	187		111	
Mean (SD)	131.95 (187.477)		151.82 (220.430)	
Median	88.00		89.00	
Min, max	49.0, 1170.0		55.0, 1130.0	
End of treatment ^a				
n	180	180	108	108
Mean (SD)	120.47 (170.496)	-13.61 (95.376)	123.78 (166.252)	-24.14 (145.731)
Median	87.00	-2.00	89.50	-1.00
Min, max	50.0, 1180.0	-826.0, 44.0	64.0, 1070.0	-949.0, 160.0
Hematocrit (fraction of 1)				
Baseline				
n	187		111	
Mean (SD)	0.26 (0.075)		0.25 (0.082)	
Median	0.27		0.27	
Min, max	0.0, 0.4		0.0, 0.4	
End of treatment ^a				
n	180	180	108	108
Mean (SD)	0.26 (0.069)	0.00 (0.046)	0.26 (0.069)	0.01 (0.061)
Median	0.27	0.00	0.27	0.00
Min, max	0.0, 0.4	-0.1, 0.3	0.0, 0.4	-0.1, 0.3
Reticulocytes (x 10¹²/L)				
Baseline				
n	175		98	
Mean (SD)	30.61 (94.719)		49.88 (118.768)	
Median	0.28		0.31	
Min, max	0.1, 430.0		0.0, 483.0	
End of treatment ^a				
n	167	164	101	95
Mean (SD)	30.08 (94.356)	-2.02 (35.862)	43.47 (112.650)	-3.24 (31.135)
Median	0.32	0.03	0.34	0.02
Min, max	0.0, 563.0	-298.0, 200.0	0.0, 566.0	-192.0, 83.0
Reticulocytes/erythrocytes (%)				
Baseline				
n	181		102	
Mean (SD)	10.26 (5.058)		10.73 (5.355)	
Median	9.20		10.00	
Min, max	1.7, 27.9		2.0, 33.6	
End of treatment ^a				
n	174	170	106	99
Mean (SD)	10.94 (5.037)	1.01 (4.898)	10.74 (4.793)	0.09 (5.399)
Median	10.70	1.05	11.00	0.30
Min, max	0.8, 26.2	-15.7, 20.2	1.4, 26.7	-19.7, 13.0

Studies included: Study 10478 and Study GLUSCC09-01.

Abbreviations: RBC = red blood cell.

^a End of treatment is the last available post-treatment observation.

Source: Copied from Applicant's ISS, table 18

The table below shows a summary of subjects with hematology parameters that shifted from baseline to end of study.

Clinical Review

NDA 208587

Endari® (L-glutamine)

Table 32: Changes in hematology parameters from baseline to end of treatment, Safety population

Parameter High or Low	L-glutamine N = 187		Placebo N = 111	
	n (%)	Potential to Shift (n)	n (%)	Potential to Shift (n)
RBC (x10 ¹² /L)				
Low	3 (27.3)	11	1 (16.7)	6
High	0	180	0	107
Hemoglobin (g/L)				
Low	5 (38.5)	13	3 (37.5)	8
High	0	170	0	100
Hematocrit (fraction of 1)				
Low	4 (100.0)	4	1 (100.0)	1
High	0	180	0	108
Reticulocytes (x10 ¹² /L)				
Low	1 (0.6)	164	0	93
High	3 (75.0)	4	5 (83.3)	6
Reticulocytes/erythrocytes (%)				
Low	0	170	0	99
High	3 (100.0)	3	4 (66.7)	6

Studies included: Study 10478 and Study GLUSCC09-01.

Abbreviations: RBC = red blood cell.

The denominators for the percentages are the number of subjects with the potential to shift.

Potential to shift to high = the number of subjects with low or normal values at baseline.

Potential to shift to low = the number of subjects with high or normal values at baseline.

Source: Copied from Applicant's ISS, table 19

All subjects in the Endari group with high or normal hematocrit values at baseline (n=4), shifted to low HCT values at the end of treatment. Of the 13 subjects in the Endari group with high or normal hemoglobin values at baseline, 5 subjects (38.5%) shifted to low at the end of treatment. For RBC count, of the 11 subjects in the Endari group with high or normal RBC values at baseline, 3 subjects (27.3%) shifted to low at the end of treatment.

Less than 1% of Endari group with high or normal reticulocyte count values at baseline, shifted to low at the end of treatment. Three out of 4 subjects (75.0%) with low or normal reticulocyte count values at baseline in the Endari group shifted to high at the end of treatment.

No subjects in the Endari or placebo groups with low or normal RBC, hemoglobin or hematocrit values at baseline shifted to high at the end of treatment.

Reviewer Comment:

Episodes of rbc hemolysis occur commonly in SCD patients. The observed high reticulocyte counts and low RBC, hematocrit and hemoglobin counts in majority of study participants is not unexpected in this study population..

Blood chemistry parameters

The table below shows the change from baseline to end of study for the serum chemistry parameters of blood urea nitrogen (BUN) and creatinine.

Table 33: Time Point Value and Change from Baseline in Serum Chemistry Parameters (Safety Population)

Clinical Review
NDA 208587
Endari® (L-glutamine)

Parameter	L-glutamine N = 187		Placebo N = 111	
	Time Point Value	Change from Screening	Time Point Value	Change from Screening
BUN (mmol/L)				
Screening				
n	185		107	
Mean (SD)	3.17 (1.501)		2.96 (2.219)	
Median	2.86		2.50	
Min, max	1.1, 11.8		0.7, 19.6	
End of treatment ^a				
n	133	133	86	82
Mean (SD)	3.41 (1.599)	0.26 (1.376)	3.27 (2.018)	0.37 (1.347)
Median	2.86	0.00	2.86	0.36
Min, max	0.7, 13.2	-4.3, 5.0	0.7, 17.1	-2.5, 5.0
Creatinine (umol/L)				
Screening				
n	186		109	
Mean (SD)	52.62 (27.019)		51.09 (30.865)	
Median	46.85		47.74	
Min, max	23.9, 248.4		19.4, 327.1	
End of study ^a				
n	133	133	86	84
Mean (SD)	51.13 (19.836)	2.21 (9.513)	50.55 (20.320)	2.92 (11.528)
Median	45.08	0.88	46.85	0.88
Min, max	20.3, 119.3	-18.6, 43.3	25.6, 170.6	-26.5, 69.0

Studies included: Study 10478 and Study GLUSCC09-01.

Source: Copied from Applicant's ISS, table 20

At baseline, the values of BUN and creatinine were similar between the Endari and placebo groups. The mean (SD) change in BUN from baseline to the end of treatment was +0.26 (1.376) mmol/L in the Endari group and +0.37 (1.347) mmol/L in the placebo group. The mean (SD) change in creatinine from baseline to the end of treatment was +2.21 (9.513) umol/L in the Endari group and +2.92 (11.528) umol/L in the placebo group.

Among subjects with high or normal BUN values at baseline, 3/118 (2.5%) subjects in the Endari group and 3/65 (4.6%) patients in placebo group shifted to low BUN values at the end of treatment. Among those with low or normal BUN values at baseline, 1/132 subjects (0.8%) in the Endari group shifted to a high BUN value at the end of treatment and no subjects in the placebo group shifted to high at the end of treatment. See table below.

Among subjects with high or normal creatinine values at baseline, 5/95 (5.3%) subjects in the Endari group and 5/61 (8.2%) patients in the placebo group shifted to low creatinine values at the end of treatment. Among patients with low or normal creatinine values at baseline, 4/129 (3.1%) subjects in the Endari group and 1/82 (1.2%) subjects in the placebo group shifted to high at the end of treatment.

Table 34: Summary of Serum Chemistry Parameters That Shifted to Low or High (Safety Population)

Clinical Review
NDA 208587
Endari® (L-glutamine)

Parameter High or Low	L-glutamine N = 187		Placebo N = 111	
	n (%)	Potential to Shift (n)	n (%)	Potential to Shift (n)
BUN				
Low	3 (2.5)	118	3 (4.6)	65
High	1 (0.8)	132	0	81
Creatinine				
Low	5 (5.3)	95	5 (8.2)	61
High	4 (3.1)	129	1 (1.2)	82

Studies included: Study 10478 and Study GLUSCC09-01.

The denominators for the percentages are the number of subjects with the potential to shift.

Potential to shift to high = the number of subjects with low or normal values at baseline.

Potential to shift to low = the number of subjects with high or normal values at baseline.

Abbreviations: BUN = blood urea nitrogen.

Source: Copied from Applicant's ISS, table 21

Review comment: Patients with uncontrolled liver disease or renal insufficiency were excluded from both studies 10478 and GLUSCC09-01. Overall, there was minimal change in the values of BUN and creatinine among Endari treated subjects over the study duration. However, since renal disease is common among patients with sickle cell disease, and Endari is eliminated at least in part by the kidneys, this reviewer agrees with the clinical pharmacology reviewer recommendation for conducting renal impairment studies for Endari in patients with severe renal abnormalities.

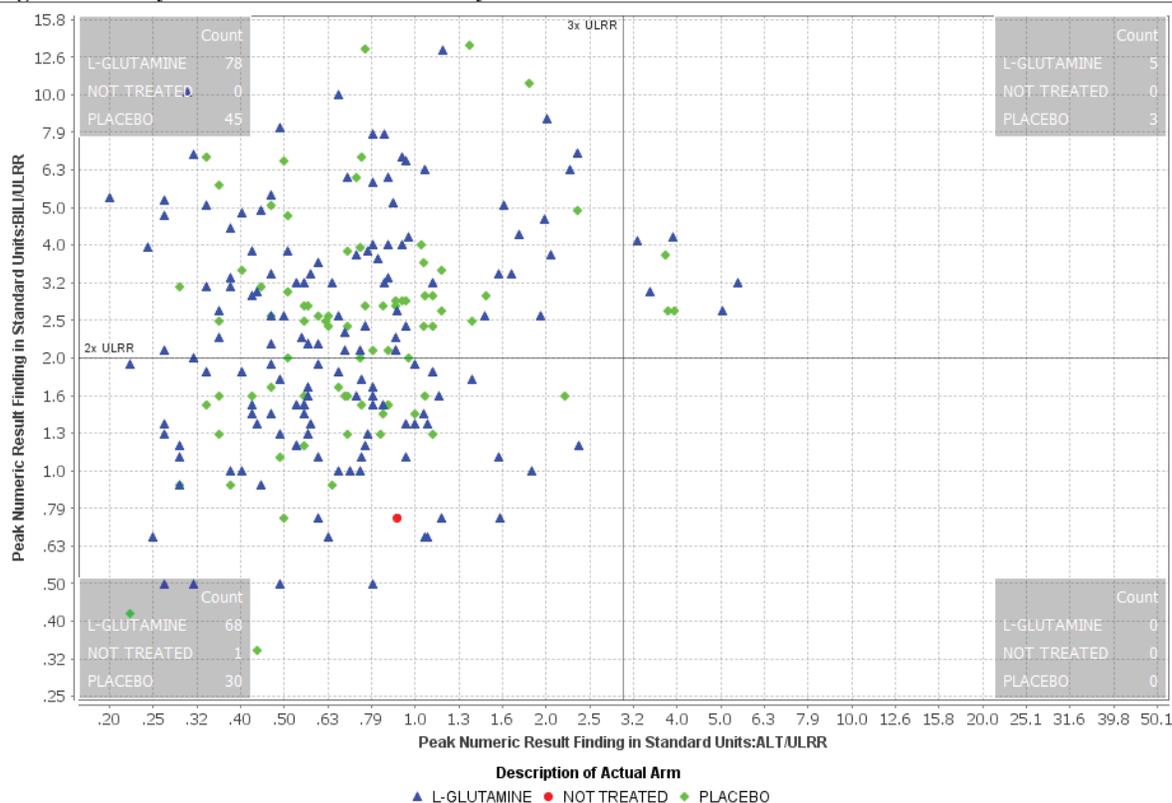
Liver Function tests

The Applicant evaluated changes from baseline to end of study for the serum chemistry parameters of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin. Overall, there were no notable differences between the Endari and placebo treatment groups.

Potentially Clinically Significant Changes in liver function tests

FDA evaluated reported liver function test results of subjects in the safety population for the occurrence of potential drug-induced liver injury. Five subjects in the Endari arm and 2 subjects in the placebo arm of Study GLUSCC0901 met the criteria for potential drug-induced liver injury (DILI), as defined by an ALT >3 times ULN, total bilirubin > 2 times ULN, and alkaline phosphatase < 2 times ULN (see Figure below). No potential cases of DLI were identified for subjects enrolled in Study 10478.

Figure 5: Study GLUSCC0901 Potential Hy's Law Plot – Total Bilirubin vs. ALT



Source: FDA analysis

Narratives of subjects in the Endari arm with potential DILI were reviewed by FDA and are summarized below.

Patient 0901-10-104 was a 15 year old male with sickle cell anemia and two sickle-cell crises in the year prior to enrollment. He also had a medical history of, splenomegaly (resolved), fever (resolved), bacteremia (resolved), and allergies. He was enrolled in Study GLUSCC09-01 and was assigned to the Endari arm 30 g/day (15 g PO TWICE DAILY) He exited the study on Study day 393.

At his baseline/screening visit, he had grade 1 elevations of ALT, AST and GGT and Grade 3 elevation of total bilirubin. At his Week 53 visit, he had grade 2 elevation of ALT, total bilirubin was reduced from baseline (but still grade 3) and alkaline phosphatase was within normal limits.

During the course of the study, he developed 7 SAEs and several non-serious adverse events. The reported SAEs for this patient were:

1. Left Elbow Effusion /Septic Joint - severe in intensity, required hospitalization, treated with antibiotics and concurrent procedure(s), resolved completely, and considered not related to study drug by the investigator;

Clinical Review

NDA 208587

Endari® (L-glutamine)

2. Fever secondary to Septic Joint - moderate in severity, a single episode, treated with concomitant medication(s), resolved and considered not related to study drug by the investigator.

The other SAEs reported for this patient were: Pain crisis - two episodes moderate in severity, , not likely related to study drug, treated with concomitant medication(s) and concurrent procedure(s), and resolved completely); Pain crisis - severe in intensity, intermittent, not related to study drug, treated with concomitant medication(s), and resolved completely; Vaso-Occlusive Crisis moderate in severity, not related to study drug, treated with concomitant medication(s), and resolved completely; and fever moderate in severity, not related to study drug, not treated, and resolved completely.

Review comment: This patient had abnormal liver enzymes at baseline which is not unexpected in sickle cell anemia patients because of the occurrence of hemolytic anemia. He also had at least 4 crises episodes during his time on study, all of which could result in worsening of his baseline hepatic insufficiency. This case is also confounded by concurrent medications used. Therefore, this reviewer cannot attribute abnormal liver enzymes in this patient to Endari treatment.

Patient 0901-17-501

15-year-old black female with sickle cell anemia enrolled in Study GLUSCC09-01. Her medical history included asthma and cholecystectomy and she treated with hydroxyurea for sickle cell disease prior to enrollment. She received Endari from Study Day 1 through Study Day 16. Her blood chemistry results at screening and at Visit 15 are showed in the table below. At her Visit 15, she was diagnosed with mild viral hepatitis.

Table 35: Laboratory results: Patient 0901-17-501

Visit Visit Date	ALT (NR: 5-20 U/L)	AST (NR: 0-41 U/L)	LD (NR: 100-275 U/L)	GGT (NR: 4-24 U/L)	Direct Bilirubin (NR: 0.0-0.4 mg/dL)	Total Bilirubin (NR: 0.1-1.2 mg/dL)
Visit 1						
Screening 13Sep2011	78[H]	102[H]	368[H]	74[H]	1.0[H]	4.3[H]
Visit 15 09Mar2012	57[H]	55[H]	382*[H]	108[H]	1.5[H]	5.0[H]

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma glutamyltransferase, H = high, LD = lactate dehydrogenase, NR = normal range.

*NR for LD: 100-200 U/L (LD had a different NR at Screening and Visit 15).

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Concomitant medications taken at the time of the viral hepatitis diagnoses included hydroxyurea, pregabalin, morphine, oxycodone hydrochloride, hydromorphone, ketorolac, salbutamol inhaler, docusate sodium and fluticasone propionate inhaler. The investigator assessed the viral hepatitis as not related to Endari. The outcome of viral hepatitis was unknown.

Clinical Review

NDA 208587

Endari® (L-glutamine)

Review Comment: *The role of Endari in causing the abnormal LFTs in this patient is unlikely because – the patient was diagnosed with viral hepatitis in the course of the study and also had abnormal liver function tests at screening prior to study drug administration. Causality assessment is further confounded by several concomitants medications on board at the Day 15 visit.*

Patient 0901-14-502 was a 14 year old Hispanic female with sickle β^0 -thalassemia enrolled in Study GLUSCC09-01. She received Endari from Study Day 1 through Study Day 363 and completed the study 7 days after the last dose of Endari. Her medical history included elevated ALT and AST, splenectomy, gastritis, pharyngitis, asthma, and acute chest syndrome. She had been treated with HU for sickle cell disease for approximately 0.5years prior to study enrollment.

The patient experienced mild intermittent upper abdominal pain on Study Day 39 which was assessed by the investigator as possibly related to Endari treatment. No concomitant medication was administered to treat this event. On Study Day 44, the abdominal pain resolved. The patient experienced 4 other episodes of mild abdominal pain on Study Days 130, 135, 214 and mild pain in extremity on study Day 215. All of these pain episodes were assessed to be unrelated to Endari treatment by the Investigator.

On Study Day 196, the patient was diagnosed with severe sickle cell anemia with crisis manifesting as pain in left thigh and knee. This crisis resolved 10 days later.

The investigator assessed this crisis event as not related to Endari. On Study Day 310, the patient experienced another severe sickle cell anemia with crisis-second occurrence. She received IV fluids for hydration and ketorolac for pain. On Study Day 316, the sickle cell anemia with crisis resolved. The investigator assessed sickle cell anemia with crisis as not related to Endari. Other events reported for this patient was intermittent constipation, pyrexia and mild pain in extremity (unrelated to study treatment).

Her blood chemistry results at screening and at Visit 15 are showed in the table below.

Table 36: Laboratory results: Patient 0901-14-502

Visit Visit Date	ALT (NR: 5-20 U/L)	AST (NR: 0-41 U/L)	LD (NR: 100-275 U/L)	GGT (NR: 4-24 U/L)	Direct Bilirubin (NR: 0.0-0.4 mg/dL)	Total Bilirubin (NR: 0.1-1.2 mg/dL)
Visit 1 Screening 28Dec2010	110[H]	91[H]	640[H]	237[H]	0.6[H]	3.5[H]
Visit 15 23Jan2012	35[H]	65[H]	743[H]	73[H]	0.4	3.8[H]

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma glutamyltransferase, H = high, LD = lactate dehydrogenase, NR = normal range.

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Concomitant medications taken in the course of the study included folic acid, Panadeine Co, hydroxyurea, seretide, montelukast sodium, ranitidine, and ibuprofen.

Review Comment: *The role of Endari in causing the abnormal LFTs in this patient cannot be determined for the following reasons: This patient had abnormal hepatic panel tests at screening*

Clinical Review

NDA 208587

Endari® (L-glutamine)

prior to study drug administration. She also had several episodes of unexplained intermittent abdominal pain which could have been hepatic sequestration events. Causality assessment is further confounded by several concomitants medications taken over the course of the study treatment period.

Patient 0901-04-101 was a 16-year-old, Black female enrolled in Study GLUSCC09-01 in the Endari treatment group. Her relevant medical history included liver enlargement, mildly icteric sclera, lactose intolerance, genital herpes simplex (type I), and splenomegaly. She had no history of treatment with HU or any other anti-sickling medication.

At screening, she had elevated levels of LDH and total bilirubin however other hepatic chemistry parameters [ALT, AST, ALP, GGT and direct bilirubin] were normal. On Study Day 57, she had thrombocytopenia (platelet count of $129 \times 10^3/\mu\text{L}$ and anemia (hemoglobin at 8.7 g/dL). She was diagnosed with moderate hypersplenism (worsening of anemia and thrombocytopenia) on Study Day 57 and moderate splenic sequestration on Study Day 65. No actions were taken with Endari due to hypersplenism and splenic sequestration. Both events (hypersplenism and splenic sequestration) were completely resolved on Study Day 71. The investigator assessed the hypersplenism and splenic sequestration as not likely related to Endari. The investigator assessed the abnormal liver function tests as not likely related to Endari. The patient's relevant laboratory results at screening and at visit 15 are shown below:

Table 37: Laboratory results: Patient 0901-04-101

Visit	ALT (NR: 5-20 U/L)	AST (NR: 0-41 U/L)	ALP (NR: 45-150 U/L)	LD (NR: 100-220 U/L)	GGT (NR: 4-24 U/L)	Direct Bilirubin (NR: 0.0-0.4 mg/dL)	Total Bilirubin (NR: 0.1-1.2 mg/dL)
Visit 1							
Screening 14Apr2011	10	19	83	278[H]	14	0.2	3.2[H]
Visit 15							
16May2012	101[H]	49[H]	108	252	77[H]	0.4	2.3[H]

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma glutamyltransferase, H = high, LD = lactate dehydrogenase, NR = normal range.

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Concomitant medications at the time of the hypersplenism and liver function test abnormal include tilactase for lactose intolerance since an unknown date, folic acid, acyclovir, morphine, oxycodone/APAP, diphenhydramine, ketorolac, docusate and ibuprofen.

The patient received her last dose of study medication on Study Day 358 and completed the study on Study Day 379.

Review Comment: Assessment of the role of Endari in causing the abnormal LFTs in this patient cannot be determined. The case is confounded because at screening, the patient had some abnormalities in liver function tests (elevated levels of LDH and total bilirubin). She also

Clinical Review

NDA 208587

Endari® (L-glutamine)

had crises episodes include splenic sequestration during the study treatment period and received several concomitants medications over the course of the study treatment period.

Patient 0901-09-514

15-year-old, Black female with sickle cell anemia enrolled in Study GLUSCC09-01 in the Endari treatment group. Her medical history included constipation, abdominal pain, gall stones, asthma, acute chest syndrome, vitamin D deficiency, anterior uveitis, and hypoxia. She had been treated with HU prior to enrollment.

At screening, she had elevated levels of ALT, AST, lactate dehydrogenase (LD), direct bilirubin, and total bilirubin. On Study Day 170, at Visit 15, the patient's laboratory results showed elevated levels GGT and LDH; however laboratory results were normal for ALT, ALP, AST, direct bilirubin and total bilirubin. Her lab results at screening and at the Visit 15 are shown below:

Table 38: Laboratory results: Patient 0901-09-514

Visit Visit Date	ALT (NR: 5-20 U/L)	AST (NR: 0-41 U/L)	ALP (NR: 110-630 U/L)	LD (NR: 100-275 U/L)	GGT (NR: 4-24 U/L)	Direct Bilirubin (NR: 0.0-0.4 mg/dL)	Total Bilirubin (NR: 0.1-1.2 mg/dL)
Visit 1 Screening 16Jul2012	69[H]	94[H]	80[L]	1165[H]	21	0.6[H]	3.6[H]
Visit 15 16Jan2013	11	18	173	569[H]	32[H]	0.4	0.8

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma glutamyltransferase, H = high, LD = lactate dehydrogenase, L = low, NR = normal range.

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The patient was diagnosed mild sickle cell anemia with crisis (vaso-occlusive crisis) on Study Day 9 and on Study Day 43. She also experienced moderate sickle cell anemia with crisis (sickle cell chest pain) on Study Day 119 and Study Day 145 along with headache and pyrexia. No actions were taken with Endari due to the headache, sickle cell anemia with crisis, and pyrexia.

On Study Day 150, the patient was hospitalized for multi-organ dysfunction. She was hypoxic and anemic. She received supportive care including IV fluids, pain medications and salbutamol sulfate for asthma. The investigator decided to start the patient on chronic transfusions and the patient was therefore discontinued from the study. The patient received her last dose of Endari on an unknown date in Dec 2012 and was discontinued from the study on Study Day 1702013. The investigator assessed the sickle cell anemia with crisis as not likely related to Endari.

Concomitant medications at the time of the sickle cell anemia with crisis included HU; folic acid, lansoprazole, montelukast sodium, levosalbutamol, ibuprofen for pain, and macrogol for constipation, Simeco for acid reflux, budesonide hydrochloride; hydrocodone, methotrexate for uveitis, vitamin D, ipratropium bromide, ondansetron hydrochloride; docusate sodium;

Clinical Review

NDA 208587

Endari® (L-glutamine)

salbutamol; naloxone hydrochloride; magnesium citrate; diphenhydramine; ceftriaxone sodium; nalbuphine; calcium; azithromycin; and cefotaxime and oseltamivir .

Review Comment: *The role of Endari in causing the abnormal LFTs in this patient cannot be determined but appears unlikely for the following reasons: this patient had abnormal liver function tests at screening prior to study drug administration. She also had several episodes of sickle cell crises during the course of the study . Causality assessment is further confounded by several concomitants medications taken over the course of the study treatment period.*

No potential cases of DLI were identified for subjects enrolled in Study 10478.

7.4.3 Vital Signs

The Applicant reported mean changes in vital signs from baseline to the end of treatment for subjects in safety population. Mean changes from baseline to end of treatment for diastolic blood pressure, temperature, pulse rate, and respiratory rate were generally similar between Endari and placebo treated patients.

Review Comment: *Since the study treatment was administered over 48 weeks and several factors may influence the vital signs of any given patient, the clinical meaningfulness of changes in vital signs from baseline to the end of treatment is of limited value.*

7.5. Other Safety Explorations

7.5.1. Dose Dependency for Adverse Events

The Applicant did not collect data on study drug dose and did not evaluate the occurrence of adverse events by dose. Since dosing in Studies 10478 and GLUSCC09-01 was weight based, FDA evaluated the occurrence of common adverse events by body weight as a proxy for dose.

In Study GLUSCC09-01, the following weight based study drug dosing scheme was used:

Weight in kgs.	Weight in lbs.	Per dose in grams	Per day in grams	Packets per dose	Packets per day
<30	<66	5.0	10.0	1	2
30-65	66-143	10.0	20.0	2	4
>65	>143	15.0	30.0	3	6

Source: Study GLUSCC09-01: Clinical trial report

In Study 10478, weight based dosing was as follows:

Weight, kg	Weight, lb	Grams Per Dose	Grams Per Day	Packets Per Dose	Packets Per Day
17 - 33.3	37.4 - 73.26	5.0	10.0	1	2
33.4 - 66.6	73.27 - 146.52	10.0	20.0	2	4
> 66.7	> 146.53	15.0	30.0	3	6

Source: Study 10478: Clinical trial report

Clinical Review

NDA 208587

Endari® (L-glutamine)

For this review, AEs by dose were evaluated using the following weight categories: <30 kg, 30 - 65 kg, 65-100 kg and ≥100 kg. This weight binning was used because although the approximate dose of Endari used in both studies 10478 and GLUSCC09-01 was 0.3g/day, the maximum daily limit was 30grams per day. Therefore, patients < 30kgs received a higher dose of study drug per kg body weight compared to those with a baseline body weight of >30kgs and those >100kg body weight received less drug per kg body weight.

At the request of FDA, the Applicant provided the tables below which show the number and percent of subjects with reported TEAEs by body weight and by study treatment group. There were no notable differences in the occurrence of reported TEAEs by baseline body weight.

Table 39: Subjects with TEAEs, by body weight, by treatment group (Safety Population)

Body weight category (kilograms)	Endari N=187		Placebo N=111	
	Number of subjects	Subjects with ≥1 TEAE, n (%)	Number of subjects	Subjects with ≥1 TEAE, n (%)
< 30	17	16 (94.1)	10	10 (100.0)
30-65	100	98 (98.0)	59	56 (94.9)
66-100	68	65 (95.6)	37	37 (100)
>100	2	1 (50.0)	5	5 (100)

Source: Applicants analysis- Response to Information Request 05/30/ 2017

The table below shows the number and percent of subjects with reported SAEs by body weight and by study treatment group. SAEs were reported in a notably lower percentage of subjects with a baseline body weight of <30kgs compared to the other baseline body weight categories.

Table 40: Subjects with SAEs, by body weight, by treatment group (Safety Population)

Body weight category (kilograms)	Endari N=187		Placebo N=111	
	Number of subjects	Subjects with ≥1 SAE, n (%)	Number of subjects	Subjects with ≥1 SAE, n (%)
< 30	17	10 (58.8)	10	9 (90.0)
30-65	100	78 (78.0)	59	46 (78.0)
66-100	68	51 (75.0)	37	29 (78.4)
>100	2	2 (100)	5	5 (100)

Source: Applicants analysis- Response to Information Request 05/30/ 2017

The following table shows SAEs reported in subjects with a baseline body weight of less than 30kgs. Among subjects with baseline body weight of <30kgs, sickle cell crises and ACS occurred in a notably higher percentage of placebo treated patients.

Table 41: SAEs occurring in Endari treated subjects with baseline body weight <30kgs

PT	Endari (n = 17)		Placebo (n = 10)	
	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Sickle cell anemia with crisis	9	52.9	9	90.0
Acute chest syndrome	3	17.6	3	30.0

Clinical Review

NDA 208587

Endari® (L-glutamine)

Pneumonia	1	5.9	0	0.0
Pyrexia	1	5.9	0	0.0
Reticulocytopenia	1	5.9	0	0.0
Rhinitis allergic	1	5.9	0	0.0

Source: FDA Analysis

Review Comment: Overall, the percentage of subjects with TEAEs was similar across body weight categories. More importantly, the frequency of SAES was considerably lower among subjects with a baseline body weight of < 30kgs who received a higher dose of study medication per kg body weight. Additionally, disease related SAES - sickle cell anemia with crises and acute chest syndrome – occurred in a notably higher proportion of subjects in the placebo group. This reviewer concludes that there is no apparent dose dependent adverse event trend in the safety population.

7.5.2. Time Dependency for Adverse Events

The Applicant did not conduct any specific analyses to evaluate time to onset of AEs. Since study drugs were administered twice daily over the entire study treatment period and given the occurrence of repeated treatment emergent adverse events for individual study subjects FDA was unable to evaluate time-dependency for adverse events.

7.5.3. Drug-Demographic Interactions

This section provides a summary of the analysis of TEAE by selected demographic variables (age and gender) for the safety population.

Age

Both Studies 10478 and GLUSCC09-01 included pediatric patients. Across both studies, 54 subjects (18.1%) were 5 to 12 years old, 74 subjects (24.8%) were 13 to 18 years old and 170 (57.0%) were >18 years old. FDA evaluated the occurrence of TEAE in the safety population by age. As shown in the following table, the percentage of subjects who reported TEAEs was similar in the Endari and placebo treatment groups for subjects in the 3 age categories (5-12 years, 13-18 years and >18 years).

Table 42: Number and percent of subjects with TEAEs by age group (5-12 years, 13-18 years and >18 years), Safety population

Age group, years	Endari N=187		Placebo N = 111	
	Number of subjects	Subjects with ≥ 1 TEAEs (%)	Number of subjects	Subjects with ≥ 1 TEAEs (%)
5-12	35	18.7	19	17.1
13-18	45	24.1	29	26.1
> 18	107	57.2	63	56.8

Source: FDA Reviewer Analysis

Clinical Review

NDA 208587

Endari® (L-glutamine)

FDA also evaluated the occurrence of TEAEs by the following age categories: ≤ 18 years old and > 18 years old. The following two tables below show a summary of TEAEs occurring in $\geq 10\%$ of Endari treated subjects in the safety population by age (≤ 18 years old and > 18 years old).

Table 43: TEAEs occurring in $\geq 10\%$ of Endari-treated subjects ≤ 18 years, (Safety Population)

PT	Endari (N = 80)		Placebo (N = 48)	
	Number of subjects	%	Number of subjects	(%)
Sickle cell anemia with crisis	67	83.7	42	87.5
Constipation	25	31.3	12	25.0
Pyrexia	22	27.5	23	47.9
Headache	21	26.3	12	25.0
Cough	20	25.0	13	27.1
Pain in extremity	18	22.5	4	8.3
Back pain	17	21.3	2	4.2
Abdominal pain	15	18.8	6	12.5
Upper respiratory tract infection	14	17.5	13	27.1
Acute chest syndrome	13	16.3	14	29.2
Nausea	13	16.3	11	22.9
Arthralgia	12	15.0	8	16.7
Chest pain	12	15.0	7	14.6
Nasal congestion	11	13.8	4	8.3
Vomiting	11	13.8	8	16.7
Oropharyngeal pain	10	12.5	7	14.6
Ocular icterus	9	11.3	5	10.4
Pruritus	9	11.3	4	8.3
Abdominal pain upper	8	10.0	3	6.3
Diarrhea	8	10.0	3	6.3

Source: FDA Reviewer Analysis

Table 44: TEAEs occurring in $\geq 5\%$ of Endari-treated subjects > 18 years, (Safety Population)

PT	Endari (N = 107)		Placebo (N = 63)	
	Number of subjects	(%)	Number of subjects	(%)
Sickle cell anemia with crisis	87	81.3	55	87.3
Nausea	23	21.5	5	7.9
Constipation	15	14.0	8	12.7
Headache	14	13.1	5	7.9
Vomiting	13	12.2	6	9.5
Pneumonia	13	12.2	12	19.1
Upper respiratory tract infection	12	11.2	7	11.1
Chest pain	11	10.3	3	4.8
Abdominal pain, upper	11	10.3	5	7.9

Clinical Review

NDA 208587

Endari® (L-glutamine)

Urinary tract infection	10	9.4	2	3.2
Nasopharyngitis	10	9.4	4	6.4
Arthralgia	10	9.4	7	11.1
Pyrexia	10	9.4	8	12.7
Cough	9	8.4	2	3.2
Diarrhea	9	8.4	4	6.4
Leukocytosis	9	8.4	5	7.9
Fatigue	8	7.5	1	1.6
Tachycardia	8	7.5	1	1.6
Pain in extremity	7	6.5	4	6.4
Anemia	7	6.5	5	7.9
Dizziness	6	5.6	1	1.6
Edema peripheral	6	5.6	3	4.8
Back pain	6	5.6	4	6.4
Ocular icterus	6	5.6	5	7.9
Hypokalemia	6	5.6	6	9.5
Acute chest syndrome	6	5.6	10	15.9

Source: FDA Reviewer Analysis

The most commonly reported TEAE among subjects who received Endari in all the age group categories was sickle cell anemia with crisis. The percentage of subjects reporting TEAEs was generally similar between the age groups in the Endari group. There were some TEAEs where a higher percentage of subjects reported that TEAE among subjects ≤ 18 years old compared with subjects > 18 years old in the Endari group: ACS (16.3% vs 5.6%), constipation (31.3% vs 14.0%), pyrexia (27.5% vs 9.3%), pain in extremity (22.5% vs 6.5%), back pain (21.3% vs 5.6%), and cough (25.0% vs 8.4%). A similar trend was seen among placebo treated subjects: acute chest syndrome (29.2% vs 15.9%), constipation (25% vs 12.7%), headache (25.0% vs 7.9%), pyrexia (47.9% vs 27.9%), nausea (22.9 vs 7.9%), and cough (27.1% vs 3.2%).

SAEs by Age

The table below shows a summary of SAEs that occurred in subjects 18 years of age and younger and those > 18 years of age, by PT in the safety population.

Table 45: SAEs occurring in $\geq 2\%$ of Endari-treated Subjects, by age group (≤ 18 versus > 18 years), Safety Population

Subjects ≤ 18 years				
PT	Endari (n=80)		Placebo (n=48)	
	Number of subjects	(%)	Number of subjects	(%)
Subjects with ≥ 1 SAEs	63	78.8	39	81.3
Sickle cell anemia with crisis	56	70.0	37	77.1
Acute chest syndrome	10	12.5	12	25.0
Pyrexia	5	6.2	3	6.2
Asthma	3	3.7	1	2.1

Clinical Review
NDA 208587
Endari® (L-glutamine)

Pneumonia	3	3.7	2	4.2
Chest pain	2	2.5	0	0
Device malfunction	2	2.5	0	0
Hypersplenism	2	2.5	0	0
Vomiting	2	2.5	1	2.1
Subjects >18years of age				
	Endari (n=107)		Placebo (n=63)	
PT	Number of subjects	(%)	Number of subjects	(%)
Subjects with ≥ 1 SAEs	78	72.9	50	79.4
Sickle cell anemia with crisis	68	63.55	43	68.3
Pneumonia	6	5.61	8	12.7
Pregnancy	4	3.74	3	4.8
Acute chest syndrome	3	2.8	9	14.3
Chest pain	3	2.8	2	3.2

Source: FDA analysis

The percentage of subjects with reported SAEs was similar for subjects ≤ 18 years of age and subjects who were > 18 years of age in the Endari group (63 subjects [78.8%] and 78 subjects [72.9%], respectively) and in the placebo group (39 subjects [81.3%] and 50 subjects [79.4%], respectively). In subjects 18 years of age or younger, again, ACS occurred in a notably higher proportion of placebo treated patients (10 subjects [12.5%] and 12 subjects [25.0%] in subjects ≤ 18 and > 18 years of age respectively. Similarly, in subjects over 18 years of age, ACS occurred in a higher proportion of placebo treated patients (3 subjects [2.8%] and 9 subjects [14.3%] of subjects' ≤ 18 and > 18 years of age respectively).

When subjects ≤ 18 years of age were split into 2 groups (5 to 12 years and 13 to 18 years of age), the percentage of subjects who reported SAEs in the Endari group was higher in subjects who were 13 to 18 years old (39 subjects [86.7%]) compared with subjects who were 5 to 12 years old (24 subjects [68.6%]). In the placebo group, the percentage of subjects who reported SAEs was slightly higher in subjects who were 5 to 12 years old (18 subjects [94.7%]) compared with subjects who were 13 to 18 years old (21 subjects [72.4%]). See table below.

Table 46: Subjects with SAEs by age group (5-12, 13-18 and >18 years), Safety population

Age group (years)	Endari (N=187)		Placebo (N = 111)	
	Number of subjects	Subjects with ≥ 1 SAEs (%)	Number of subjects	Subjects with ≥ 1 SAEs (%)
5-12	35	24 (68.6)	19	18 (94.7)
13-18	45	39 (86.7)	29	(72.4)
> 18	107	78 (72.9)	63	50 (79.4)

Source: FDA analysis

Clinical Review

NDA 208587

Endari® (L-glutamine)

Review Comment: Although some TEAEs occurred at a much higher frequency in pediatric vs adult patients treated with Endari [ACS (16.3% vs 5.6%), constipation (31.3% vs 14.0%), pyrexia (27.5% vs 9.3%), pain in extremity (22.5% vs 6.5%), back pain (21.3% vs 5.6%), and cough (25.0% vs 8.4%)], a similar pattern was observed in placebo treated patients. Therefore, it is unlikely that the observed differences in adverse events are attributable to Endari. The higher percentage of reported SAEs among Endari treated subjects 13 to 18 years old (86.7%) compared with subjects who were 5 to 12 years old (68.6%) and the higher percentage of SAEs among placebo treated patients 5-12 years of age (94.7%) is counterintuitive. The smaller numbers of subjects in these age categories precludes any meaningful conclusion from these analysis.

Sex

TEAEs by Sex

The table below shows TEAEs occurring in $\geq 5\%$ of male or female subjects in the Endari group, by PT. The percentage of subjects who reported TEAEs was similar for male and female subjects in the Endari group (83 subjects [98.8%] and 97 subjects [94.2%], respectively) and the placebo group (53 subjects [100.0%] and 55 subjects [94.8%], respectively).

Table 47: TEAEs occurring in $\geq 5\%$ of Endari treated subjects by PT, and by Sex (Safety Population)

PT	Male n= 84		Female n=53	
	Endari		Placebo	
	Number of subjects	%	Number of subjects	%
Sickle cell anemia with crisis	69	82.1	47	88.7
Constipation	17	20.2	8	15.1
Headache	16	19.0	9	17.1
Pyrexia	16	19.0	17	32.1
Cough	12	14.3	7	13.2
Back pain	11	13.1	1	1.9
Ocular icterus	11	13.1	6	11.3
Arthralgia	10	11.9	9	17.0
Upper respiratory tract infection	10	11.9	6	11.3
Acute chest syndrome	9	10.7	10	18.9
Chest pain	9	10.7	5	9.4
Pain in extremity	9	10.7	1	1.9
Diarrhea	8	9.5	3	5.7
Nausea	8	9.5	8	15.1
Abdominal pain upper	7	8.3	2	3.8
Fatigue	6	7.2	0	0
Leukocytosis	6	7.2	4	7.6
Oropharyngeal pain	6	7.2	5	9.4
Pruritus	6	7.2	4	7.6
Vomiting	6	7.2	5	9.4

Clinical Review
NDA 208587
Endari® (L-glutamine)

<i>Female</i>	<i>N=103</i>		<i>n=58</i>	
	<i>Number of subjects</i>	<i>%</i>	<i>Number of subjects</i>	<i>%</i>
Sickle cell anemia with crisis	85	82.5	50	86.2
Nausea	28	27.2	8	13.8
Constipation	23	22.3	12	20.7
Headache	19	18.5	8	13.8
Vomiting	18	17.5	9	15.5
Cough	17	16.5	8	13.8
Pain in extremity	16	15.5	7	12.1
Pyrexia	16	15.5	14	24.1
Upper respiratory tract infection	16	15.5	14	24.1
Abdominal pain	14	13.6	3	5.2
Chest pain	14	13.6	5	8.6
Abdominal pain upper	12	11.6	6	10.3
Arthralgia	12	11.6	6	10.3
Back pain	12	11.6	5	8.62
Nasopharyngitis	11	10.7	6	10.3
Pneumonia	11	10.7	8	13.8
Urinary tract infection	11	10.7	3	5.2
Acute chest syndrome	10	9.7	14	24.1
Diarrhea	9	8.7	4	6.9
Dyspnea	7	6.8	5	8.62
Nasal congestion	7	6.8	3	5.2
Pruritus	7	6.8	5	8.6
Anemia	6	5.8	3	5.2
Oropharyngeal pain	6	5.8	7	12.1

Source: FDA analysis

The most commonly reported TEAE among all subjects who received Endari for both male and female subjects was sickle cell anemia with crisis. Other than nausea which was reported in a higher percentage of female (28 subjects [27.2%]) versus male subjects (8 subjects [9.5%]) in the Endari group; the percentage of subjects reporting all other TEAEs was generally similar between male and female subjects for the Endari group.

SAEs by Sex

The frequency of reported SAEs was similar for male and female subjects in the Endari group (62 subjects [73.8%] and 79 subjects [76.7%], respectively). The most commonly reported SAE among both male and female subjects who received Endari was sickle cell anemia with crisis. See table below.

SAEs in ≥ 2% of Endari treated subjects by PT, and by Sex (Safety Population)

	Endari		Placebo	
<i>Male</i>	<i>n=84</i>		<i>n=53</i>	
PT	Number of subjects	%	Number of subjects	%
Sickle cell anemia with crisis	55	65.5	40	75.5
Acute chest syndrome	6	7.1	8	15.1
Pneumonia	3	3.6	6	11.3
Pyrexia	3	3.6	2	3.8
Influenza	2	2.4	1	1.9
Transient ischemic attack	2	2.4	0	0
<i>Female</i>	<i>n=103</i>		<i>n=58</i>	
PT	Number of subjects	%	Number of subjects	%
Sickle cell anemia with crisis	69	70.0	40	70.0
Acute chest syndrome	7	6.8	13	22.4
Pneumonia	6	5.8	4	6.9
Chest pain	4	3.9	2	3.5
Pregnancy	4	3.9	3	5.2
Asthma	3	2.9	2	3.5

Source: FDA analysis

Five female subjects (4.9%) in the Endari group reported TEAEs that led to withdrawal. These events were: hypersplenism, abdominal pain, dyspepsia, burning sensation, pregnancy, and hot flush. No male subjects reported TEAEs that led to withdrawal in the Endari group.

Reviewer Comment: There are no notable differences in the occurrence of TEAEs or SAEs by sex for Endari treated patients.

Race

The majority (97%) of the subjects in the safety population were black or African American. The Applicant provided a summary of TEAEs, SAEs, and TEAEs that led to withdrawal by race (results not shown). Overall, there were no notable differences in the frequency of reported TEAEs, SAEs, or TEAEs that led to withdrawal by race in the Endari or placebo treatment group.

Reviewer Comment: The race distribution of the safety population is not unexpected because in the United States, SCD most commonly affects blacks/African-Americans. This reviewer agrees with the Applicant that the small number of subjects in the other racial category precludes any meaningful comparisons between the races.

Clinical Review

NDA 208587

Endari® (L-glutamine)

7.5.4. Drug-Disease Interactions

The Applicant provided a summary of TEAEs, SAEs, and TEAEs that led to withdrawal by diagnosis at baseline (sickle cell anemia or sickle β^0 -thalassemia). There were no notable differences in the percentage of subjects who reported TEAEs, SAEs, or TEAEs that led to withdrawal between subjects by baseline diagnosis. FDA agrees with the Applicant that the small number of subjects with a diagnosis of sickle β^0 -thalassemia preclude any meaningful comparisons between the diagnosis categories.

Hydroxyurea (HU) use

In both Studies 10478 and GLUSCC09-01, use of the approved anti-sickling agent, hydroxyurea, was permitted. In Study GLUSCC0901 randomization was stratified by HU use. FDA evaluated the occurrence of TEAEs and SAEs in by HU use at baseline in the safety population.

Table 48: AEs by Hydroxyurea (HU) use

	Endari N = 187		Placebo N = 111	
	HU use at baseline n=124	No HU use at baseline n=63	HU use at baseline n=65	No HU use at baseline n=46
Subjects with at least 1,				
TEAEs, n (%)	122 (98.4)	58 (92.1)	65 (100.0)	43 (93.5)
TEAEs leading to withdrawal from study, n (%)	2 (1.6)	3(4.8)	1 (1.5)	0
SAE, n (%)	100 (80.6)	41 (65.1)	57 (87.7)	32 (69.6)
Sickle cell anemia with crisis	107 (86.3)	45 (71.4)	60 (92.3)	37 (80.4)

Source: FDA analysis

Among subjects treated with Endari, the percentage of subjects who reported TEAEs was similar for subjects with HU use at baseline and those without hydroxyurea use at baseline (122 subjects [98.4%] and 58 subjects [92.1%], respectively). The most commonly reported TEAE among Endari treated subjects with or without hydroxyurea use at baseline was sickle cell anemia with crisis.

The percentage of subjects who reported SAEs was slightly higher for subjects with hydroxyurea use at baseline compared with subjects without hydroxyurea use at baseline in the Endari group (100 subjects [80.6%] and 41 subjects [65.1%], respectively). The most commonly reported SAE among all subjects was sickle cell anemia with crisis: reported in a higher percentage of subjects with hydroxyurea use at baseline compared with subjects without hydroxyurea use at baseline in the Endari group (90 subjects [72.6%] and 34 subjects [54.0%], respectively) and in the placebo group (51 subjects [78.5%] and 29 subjects [63.0%], respectively).

Review comment: The reason for the higher reported frequency of sickle cell anemia with crisis in HU users among Endari treated subjects is unclear. A similar trend occurred among placebo treated subjects. This could possibly be related to a higher likelihood of seeking medical care or reporting AEs in HU users versus non users. These data should be interpreted with caution since HU use at baseline was not balanced at baseline in Study 10478.

7.5.5. Drug-Drug Interactions

No drug-drug interaction studies with Endari were conducted. The Applicant provided a summary of several published nonclinical studies that examined the effects of combining L-glutamine with other agents such as: indomethacin, cyclosporine, methotrexate, 5-fluorouracil and dexamethasone. The Applicant reported that in these studies, L-glutamine treatment did not cause any detrimental effects and generally alleviated deleterious side effects normally caused by these agents.

Reviewer Comment: The adequacy of the referenced drug-drug interaction studies from the published literature is deferred to the clinical pharmacology reviewer.

7.6. Additional Safety Evaluations

7.6.1. Human Carcinogenicity

No long-term animal studies or clinical data on the human carcinogenicity of Endari was submitted in this application. This should be reflected in the label for Endari.

The need for carcinogenicity studies for Endari is deferred to the Pharmacology/Toxicology reviewer.

7.6.2. Human Reproduction and Pregnancy Data

No clinical data on the use of Endari during pregnancy was submitted in this application. The Applicant reported that, it is not known whether glutamine can cause fetal harm when administered to a pregnant woman or whether glutamine can affect reproductive capacity.

FDA searched the Medline (PubMed) database for publications on glutamine supplementation during pregnancy in humans. One relevant study (Devreker, Winston et al. 1998) was identified. This was a randomized, controlled, prospective study of 138 normally fertilized and non-transferred human embryos obtained from couples undergoing in-vitro fertilization treatment. On day 2 after fertilization, the embryos were randomly allocated to one of two glucose-free mediums with or without 1 mM of glutamine. The investigators reported that, supplementation with glutamine is beneficial for human preimplantation embryo development in vitro, and increases the proportion of embryos that develop to the morula and blastocyst stages.

Reviewer Comment: There is no clinical data evaluating the safety of Endari use during pregnancy. This should be reflected in the drug label.

7.6.3. Pediatrics and Assessment of Effects on Growth

Both Studies 10478 and GLUSCC09-01 included pediatric subjects. Height and weight of study subjects were measured at each visit; however, the Applicant's Integrated Safety database did not include data on changes in height, weight or growth curve. The Applicant reported that, the number of patients for whom height and weight were reported for this study varied by visit.

Clinical Review

NDA 208587

Endari® (L-glutamine)

For Study GLUSCC09-01: The average height at Week 0 among subjects less than 20 years of age in the Endari and placebo groups was 151.5 and 149.7 cm respectively. The Applicant reported no statistically significant between-group differences in mean change from baseline to Week 48: mean change from baseline was +3.3 cm in the Endari group and +3.2 cm in the placebo group.

For patients less than 20 years of age, the average weight at Week 0 was 47.3 and 45.1 kg among subjects in the Endari and placebo groups respectively. The Applicant reported that, for these patients, there was no statistically significant between-group differences in weight change from baseline (mean change from baseline was +2.6 kg in the Endari group and +2.8 kg in the placebo group at Week 48).

Per the Applicant, eight patients (four in the Endari group and four in the placebo group) had growth curve shifts of two percentile groups from screening to study exit. For most children, the height and weight percentiles either stayed the same or showed a slight increase or decrease over the course of the study.

For Study 10478: The average height at Week 0 among subjects in the Endari and placebo groups was 169.8 and 169.2 cm respectively. The Applicant reported no statistically significant between-group differences in mean change from baseline to Week 48.

The average weight at Week 0 among subjects in the Endari and placebo group was 67.1 and 70.7 kg respectively. Mean changes in weight from baseline ranged from -1.0 to +2.6 kg in the Endari group and from -0.4 to +4.0 kg in the placebo group. The only statistically significant difference occurred at Week 12 when a mean increase in weight of 1.6 kg was reported in the Endari group compared to a mean decrease of 0.4 kg in the placebo group ($p = 0.009$). The Applicant reported that data on growth curves based on height or weight were available for too few patients in each treatment group for any meaningful conclusions to be drawn.

Review comment: The data provided does not demonstrate any notable effects of Endari on height or weigh of study participants. However, there is insufficient data available to allow any meaningful evaluation of the effect of Endari treatment on growth in pediatric subjects.

7.6.4. Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no events in the ISS adverse events data file pertaining to an overdose of Endari.

The Applicant reported that, single oral doses of glutamine at about 20 to 22 g/kg, 8 to 11 g/kg, and 19 g/kg were lethal in mice, rats, and rabbits, respectively.

7.6.5. Hepatotoxicity

Studies GLUSCC09-01 and 10478 excluded patients with uncontrolled liver disease. Metabolism is the major route of elimination for L-glutamine. The need for hepatic impairment studies for Endari in patients with SCD is deferred to the Clinical Pharmacology reviewer.

Clinical Review

NDA 208587

Endari® (L-glutamine)

The safety of Endari has not been studied or established in patients with hepatic impairment. This should be reflected in the label for Endari.

7.7. Additional Safety Issues

7.7.1. Literature Review

Applicants Literature review

The Applicant reported that:

- From August 1 2008 to June 10, 2011: 6 studies were identified in which subjects were exposed to L-glutamine. These literature reports did not include case reports of any individuals who experienced AEs related to L-glutamine administration during the studies.
- From June 11 2011 to June 10 2015: 39 studies were identified in which subjects were exposed to L-glutamine however none of the glutamine used in any of the studies was NutreStore. One study did not identify the source of the glutamine. These literature reports did not include any reports of any individuals who experienced AEs related to L-glutamine administration during the studies.
- From June 11 2015 to June 10 2016: 6 studies were identified in which subjects were exposed to L-glutamine however none of the glutamine used in these studies was NutreStore and was given on its own or in combination with other supplements. One paper did not identify the source of the glutamine used. None of the studies reported any adverse events that were attributable to the study medication or the L-glutamine supplement.

FDA's Literature review

FDA searched the Medline (PubMed) database to identify studies evaluating the safety of L-glutamine in general. The primary search was conducted using the term:

("glutamine"[MeSH Terms] OR "glutamine"[All Fields] OR "l glutamine"[All Fields]) AND ("safety"[MeSH Terms] OR "safety"[All Fields])

One hundred and thirty-one publications were identified by this search. The following types of publications were excluded: non-English publications, non-human publications, review articles, studies where adverse event data was not collected and publications where the safety of L-glutamine or glutamine was not directly assessed.

Sixteen relevant publications were identified and are summarized below:

- 1. Ziegler TR, et al. Efficacy and Safety of Glutamine-supplemented Parenteral Nutrition in Surgical ICU Patients: An American Multicenter Randomized Controlled Trial. *Ann Surg.* 2016 Apr;263(4):646-55.**

The goal of this randomized, controlled clinical trial (Ziegler, May et al. 2016) was to determine whether glutamine (GLN)-supplemented parenteral nutrition (PN) improves clinical outcomes in surgical intensive care unit (SICU) patients. This study was conducted in 150 adults after

Clinical Review

NDA 208587

Endari® (L-glutamine)

gastrointestinal, vascular, or cardiac surgery requiring PN and SICU care. All subjects received isonitrogenous, isocaloric PN: control subjects (n=75) received standard GLN-free PN whilst the GLN group (n=75) received PN containing alanyl-GLN dipeptide (0.5 g/kg/d). Enteral nutrition (EN) was advanced and PN weaned as needed. The primary endpoints were hospital mortality and infections.

Safety findings: Eleven hospital deaths (14.7%) occurred in the GLN-PN group compared to 13 deaths (17.3%) in the STD-PN group; difference, -2.6%, p=0.66. The 6-month cumulative mortality was 31.4% in the GLN-PN group and 29.7% in the STD-PN group (p=0.88). Incident bloodstream infection rate in the GLN-PN and STD-PN groups was 9.6 and 8.4 per 1000 hospital days, respectively (P=0.73). Other clinical outcomes and adverse events were similar.

Safety Conclusion(s): Glutamine supplemented PN was safe and did not alter clinical outcomes in SICU patients.

2. Samocha-Bonet D, et al. Glycemic effects and safety of L-Glutamine supplementation with or without sitagliptin in type 2 diabetes patients-a randomized study. *PLoS One*. 2014 Nov 20;9(11)

The goal of this study (Samocha-Bonet, Chisholm et al. 2014) was to assess the efficacy and safety of daily glutamine supplementation with or without the dipeptidyl peptidase (DPP)-4 inhibitor sitagliptin in patients with well-controlled type 2 diabetes. In this randomized cross-over study, patients with Type 2 diabetes treated with metformin (n=13, 9 men) with baseline glycated hemoglobin (HbA1c) of 7.1±0.3% (54±4 mmol/mol) were randomized to glutamine (15 g twice daily) plus sitagliptin (100 mg/d) or glutamine (15 g twice daily) plus placebo for 4 weeks.

Safety results: Blood urea increased in patients treated with glutamine (15 g twice daily) plus sitagliptin compared to the placebo group (p<0.001) without a significant time-treatment interaction (P=0.8), but creatinine and estimated glomerular filtration rate (eGFR) were unchanged (p≥0.5). Red blood cells, hemoglobin, hematocrit, and albumin modestly decreased (p≤0.02), without significant time-treatment interactions (p≥0.4). Body weight and plasma electrolytes remained unchanged (p≥0.2).

Safety Conclusion(s): Daily oral supplementation with glutamine (with or without sitagliptin) for 4 weeks decreased glycaemia in well-controlled type 2 diabetes patients, and was associated with mild plasma volume expansion.

3. Struijs MC. et al. Efficacy and safety of a parenteral amino acid solution containing alanyl-glutamine versus standard solution in infants: a first-in-man randomized double-blind trial. *Clin Nutr*. 2013 Jun;32(3):331-7

The goal of this study (Struijs, Schaible et al. 2013) was to demonstrate the safety and efficacy of a newly developed parenteral amino acid (AA) solution containing alanyl-glutamine (GLN-AA) compared to Standard-AA in pediatric subjects. In this randomized (2:1), double-blind, multicenter pilot trial, post-surgical infants were randomized to receive GLN-AA or Standard-AA solution over a minimum of 5 days to maximum of 10 days. AA profiles in blood samples

Clinical Review

NDA 208587

Endari® (L-glutamine)

obtained at baseline, day 7, and end of treatment were compared to normal ranges. Data regarding safety, and efficacy were collected.

Safety results: There were no clinical or statistical differences in adverse events, safety and efficacy parameters between both groups.

Safety Conclusion(s): Parenteral GLN-AA solution is safe in infants after surgical interventions, and is well tolerated.

4. Sufit A, et al. Pharmacologically dosed oral glutamine reduces myocardial injury in patients undergoing cardiac surgery: a randomized pilot feasibility trial. JPEN J Parenter Enteral Nutr. 2012 Sep;36(5):556-61.

The goal of this study (Sufit, Weitzel et al. 2012) was to determine if pharmacologically dosed, preoperative oral Glutamine (GLN) attenuates myocardial injury in cardiac surgery patients. In this randomized, double-blind, pilot trial, patients undergoing elective cardiac surgery, requiring cardiopulmonary bypass, were randomized to receive 25 g twice of oral alanyl-glutamine (GLN; n = 7) or maltodextrin (CONT; n = 7) daily for 3 days preoperatively. Serum troponin (TROP I), creatine kinase (CK-MB), and myoglobin (MG) were measured at multiple perioperative time points. Clinical outcomes were recorded and assessed.

Safety results: No adverse effects from the study treatments were reported. GLN supplementation significantly reduced pooled clinical complications vs CONT (p = .03).

Safety Conclusion(s): Pharmacologically dosed oral GLN therapy prior to cardiac surgery was safe and well tolerated. GLN therapy reduced myocardial injury and clinical complications.

5. Borges Dock-Nascimento D, et al. Safety of oral glutamine in the abbreviation of preoperative fasting: a double-blind, controlled, randomized clinical trial. Nutr Hosp. 2011 Jan-Feb;26(1):86-90.

The goals of this study were to investigate: 1) the safety of the abbreviation of preoperative fasting to 2 h with a carbohydrate-L-glutamine-rich drink; and 2) the residual gastric volume (RGV) after the induction of anesthesia for laparoscopic cholecystectomies. In this randomized controlled trial, 56 women (42 (17-65) years-old) scheduled for elective laparoscopic cholecystectomy were randomized to receive either conventional preoperative fasting of 8 hours (fasted group, n = 12) or one of three different beverage drinks in the evening before surgery (400 mL) and 2 hours before the initiation of anesthesia (200 mL). The beverages were water (placebo group, n = 12), 12.5% (240 mOsm/L) maltodextrin (carbohydrate group, n = 12) or the latter plus 50 g of L-glutamine (glutamine group, n = 14). A 20 F nasogastric tube was inserted immediately after the induction of general anesthesia to aspirate and measure the RGV.

Safety results: None of the patients had either regurgitation during the induction of anesthesia or postoperative complications. The RGV was similar between all study groups (p = 0.29).

Safety Conclusion(s): Abbreviation of preoperative fasting to 2hours with carbohydrate and L-glutamine is safe and does not increase the residual gastric volume during induction of anesthesia.

6. Galera SC, et al. The safety of oral use of L-glutamine in middle-aged and elderly individuals. Nutrition. 2010 Apr;26(4):375-81.

The goal of this study (Galera, Fechine et al. 2010) was to evaluate the safety of nutraceutical oral administration of L-glutamine in middle-aged and elderly individuals. In this randomized, crossover, double-blind clinical study, 30 residents of a long-term-care institution were enrolled. Fourteen subjects were randomized to receive oral L-glutamine, 0.5 g kg(-1) d(-1) and 16 subjects received calcium caseinate for 14 days. Following a 5 day washout period, supplements were switched for the second 14-d trial. Hepatic and renal functions and ammonia were performed and the estimated glomerular filtration rate (eGFR) was evaluated.

Safety results: No adverse clinical effects or clinically significant laboratory changes were noted during L-glutamine supplementation. There was no difference in ammonia levels between the study groups. There were statistically but not clinically significant increases in plasma urea nitrogen and creatinine concentrations between study groups. There was a statistically significant decrease in eGFR after L-glutamine supplementation (-13.3%) however, this was well below the 25% limit for biologic significance.

Safety Conclusion(s): L-glutamine supplementation was associated with some increases in serum urea nitrogen and creatinine and decrease in middle-aged and elderly subjects.

7. Mok E. et al. Lack of functional benefit with glutamine versus placebo in Duchenne muscular dystrophy: a randomized crossover trial. PLoS One. 2009;4(5):e5448.

The goal of this study (Mok, Letellier et al. 2009) was to evaluate the functional benefit of 4 months oral glutamine in Duchenne muscular dystrophy (DMD). In this double-blind, randomized crossover trial, 30 ambulant DMD boys were randomized to 2 intervention periods: glutamine (0.5 g/kg/d) and placebo, 4 months each, separated by a 1-month wash-out, at 3 outpatient clinical investigation centers in France. The effect of glutamine supplementation on functional benefit was assessed by comparing the change in walking speed at 4 months between the treatment groups. Secondary outcome measures included: safety.

Safety results: Subjects receiving glutamine or placebo showed no deterioration in functional measures over the course of the 9-month trial. No differences in muscle mass, markers of protein breakdown or serum creatine phospho-kinase were observed, except for a blunted increase in fat free mass in the glutamine group which led to a greater increase in fat mass percentage.

Safety Conclusion(s): Glutamine was safe and well-tolerated.

8. Juang P. et al. Enteral glutamine supplementation in critically ill patients with burn injuries: a retrospective case-control evaluation. Pharmacotherapy. 2007 Jan; 27(1): 11-9.

The goal of this retrospective case-control descriptive study (Juang, Fish et al. 2007) was to evaluate the clinical application of enteral glutamine supplementation in critically ill patients and compare the frequency of nosocomial infections in these patients with a historical control group in a burn intensive care unit (BICU). The study also assessed lengths of stay in the hospital and

Clinical Review

NDA 208587

Endari® (L-glutamine)

BICU, mortality rates, and safety profile of glutamine. Outcomes of seventeen patients receiving enteral glutamine supplementation and 15 historical control patients who were admitted to the BICU for thermal burn injuries were compared.

Safety results: The mean number of infections and the number of gram-negative infections between the glutamine and control groups were similar. Bloodstream infections occurred more frequently in the glutamine group (24 vs 8 patients, $p=0.0006$); however, cellulitis (4 vs 11, $p=0.05$) and pneumonia (9 vs 15, $p=0.15$) occurred less often. BICU length of stay (17.9 vs 15.3 days, $p=NS$), hospital length of stay (32.3 vs 26 days, $p=NS$), and mortality rates (0% vs 6.7%, $p=NS$) were similar between groups. No adverse events were attributed to glutamine supplementation.

Safety Conclusion(s): Enteral glutamine supplementation was not associated with a change in the cumulative rate of infectious complications compared with the control group, but attributed to more bloodstream infections and fewer cases of pneumonia and cellulitis.

9. Peterson DE, Jones JB, Petit RG 2nd. Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. *Cancer*. 2007 Jan 15;109(2):322-31.

The goal of study (Peterson, Jones et al. 2007) was to evaluate the efficacy and safety of Saforis (glutamine) powder for the prevention and treatment of Oral mucositis (OM). Three hundred twenty-six patients with \geq grade 2 OM during a chemotherapy screening cycle were randomized to Saforis ($n = 163$) or placebo ($n = 163$) administered 3 times/day during their next chemotherapy cycle (Treatment Cycle 1).

Safety results: Compared with placebo, Saforis (glutamine) powder significantly reduced the incidence of clinically significant \geq grade 2 OM (38.7% vs. 49.7%; $P = .026$) and severe \geq grade 3 OM (1.2% vs. 6.7%; $P = .005$) in Treatment Cycle 1. The incidence of treatment-emergent adverse events was similar between groups.

Safety Conclusion(s): The authors concluded that Saforis is safe and effective for preventing and treating OM in patients receiving mucotoxic cancer chemotherapy.

10. Cerchietti LC, et al. Double-blinded, placebo-controlled trial on intravenous L-alanyl-L-glutamine in the incidence of oral mucositis following chemoradiotherapy in patients with head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2006 Aug 1;65(5):1330-7.

The goal of this double-blinded, placebo-controlled study (Cerchietti, Navigante et al. 2006) was to determine the safety and efficacy of L-alanyl-L-glutamine for the prevention of mucositis in patients with head-and-neck cancer. Thirty-two patients with head-and-neck cancer were treated with chemoradiotherapy were randomized to receive either intravenous L-alanyl-L-glutamine 0.4 g/kg weight/day or an equal volume of saline (placebo) during chemotherapy days.

Safety results: There was a significant difference in incidence of mucositis in patients receiving placebo compared with those who received L-alanyl-L-glutamine ($p = 0.035$). No adverse effects related to the drug or the infusions were noted in either group.

Clinical Review

NDA 208587

Endari® (L-glutamine)

Safety Conclusion(s): Intravenous L-alanyl-L-glutamine may be an effective for reducing the severity of mucositis in patients with head-and-neck cancer receiving CRT. No safety signal identified.

11. Poindexter BB. Et al. Parenteral glutamine supplementation does not reduce the risk of mortality or late-onset sepsis in extremely low birth weight infants. Pediatrics. 2004 May;113(5):1209-15.

The goal of this study (Poindexter, Ehrenkranz et al. 2004) was to assess the safety and efficacy of early PN supplemented with glutamine in decreasing the risk of death or late-onset sepsis in ELBW infants. In this multicenter, randomized, double-blinded, clinical trial, 1432 extremely low birth weight infants (birth weigh 401 to 1000 g) were randomized within 72 hours of birth to receive either TrophAmine (control) or an isonitrogenous study amino acid solution with 20% glutamine whenever they received parenteral nutrition (PN) up to 120 days of age, death, or discharge from the hospital. The primary outcome was death or late-onset sepsis.

Safety results: Of the 721 infants assigned to glutamine supplementation, 370 (51%) died or developed late-onset sepsis, compared with 343 of the 712 infants (48%) assigned to control (relative risk: 1.07; 95% CI: 0.97-1.17). Glutamine had no effect on tolerance of enteral feeds, necrotizing enterocolitis, or growth. Glutamine supplementation was not associated with significant adverse events.

Safety Conclusion(s): In extremely low birth weight infants, parenteral glutamine supplementation did not decrease mortality or the incidence of late-onset sepsis.

12. Thompson SW, McClure BG, Tubman TR. A randomized, controlled trial of parenteral glutamine in ill, very low birth-weight neonates. J Pediatr Gastroenterol Nutr. 2003 Nov;37(5):550-3

The goal of this study (Thompson, McClure et al. 2003) was to assess the safety and benefits of parenteral glutamine in ill, preterm neonates. Thirty-five hospitalized preterm neonates with a birth-weight of <1000 g were randomized to receive either glutamine-supplemented parenteral nutrition (PN) (n = 17) or standard PN (n = 18).

Safety results: There were no significant differences between the groups with respect to white cell count, differential white cell count, blood urea nitrogen, plasma ammonia, lactate, pyruvate, plasma glutamine, or glutamate. The number of episodes of culture-positive sepsis or age at discharge did not differ between groups.

Safety Conclusion(s): Parenteral glutamine was well tolerated and safe in ill, pre-term neonates in this study.

13. Jian ZM et al. The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: a randomized, double-blind, controlled study of 120 patients. J Parenter Enteral Nutr. 1999 Sep-Oct;23(5 Suppl):S62-6.

Clinical Review

NDA 208587

Endari® (L-glutamine)

The goal of this study (Jian, Cao et al. 1999) was to evaluate the impact of alanyl-glutamine (Ala-Gln)-supplemented parenteral nutrition (PN) on clinical safety, nitrogen balance, intestinal permeability, and clinical outcomes in postoperative patients. In this double-blind randomized study, 120 patients undergoing major abdominal surgery were enrolled. All patients received isonitrogenous (0.20 g/kg body wt. per day) and isocaloric (30 kcal/kg body wt. per day) parenteral nutrition. In addition, the study group received Ala-Gln 0.50 g/kg per day. Safety outcomes included hospital stay and infection rate.

Safety results: Vital signs and clinical chemical parameters were similar between groups. All the patients recovered without incision infection. Hospital stay duration in the study group was 12.5 days, which was 4 days less than that of the control group ($p = .02$).

Safety Conclusion(s): Ala-Gln-supplemented PN was clinically safe. Duration of hospitalization was shorter in patients who received Ala-Gln parenteral nutrition.

14. Lacey, JM et al. The effects of glutamine-supplemented parenteral nutrition in premature infants. JPEN J Parenter Enteral Nutr. 1996 Jan-Feb;20(1):74-80.

The goals of this study (Lacey, Crouch et al. 1996) were to (1) confirm the safety of glutamine supplementation for premature infants and (2) to examine the effects of glutamine-supplemented parenteral nutrition on length of stay, days on total parenteral nutrition (TPN), days on the ventilator, and other clinical outcomes. In this prospective, randomized, double-blind trial, 44 premature infants (birth weight range: 530 to 1250 g) received either standard or glutamine-supplemented TPN and were monitored for various health and biochemical indices.

Safety results: There was a tendency toward a shorter length of stay in the NICU (73 vs 90 days, NS) in glutamine supplemented infants compared to the standard group. These findings were not observed in the infants ≥ 800 g ($n = 20$).

Safety Conclusion: Glutamine appeared to be safe for use in premature infants in this study.

15. Hornsby-Lewis L et al. L-glutamine supplementation in home total parenteral nutrition patients: stability, safety, and effects on intestinal absorption. JPEN J Parenter Enteral Nutr. 1994 May-Jun;18(3):268-73

The goal of this study (Hornsby-Lewis, Shike et al. 1994) was to determine safety and efficacy of L-glutamine when added to total parenteral nutrition (TPN) solutions of patients receiving TPN at home. The daily TPN solutions of seven patients receiving TPN at home were then supplemented with glutamine at a dose of 0.285 g/kg of body weight for 4 weeks.

Safety results: Five patients received the full 4 weeks of glutamine-TPN. In two patients, administration of glutamine-TPN mixtures was stopped at the end of week 2 and week 3 because of elevations in liver enzymes. A third patient's liver enzymes were elevated at the end of week 4. These abnormalities resolved after discontinuation of the glutamine-TPN solution.

Safety Conclusion(s): Supplementation of home TPN solutions at the dose of 0.285 g/kg of body weight was associated with some reversible hepatic toxicity. No other adverse effects were observed.

Clinical Review

NDA 208587

Endari® (L-glutamine)

16. Lowe, DK et al. Safety of glutamine-enriched parenteral nutrient solutions in humans. *Am J Clin Nutr.* 1990 Dec;52(6):1101-6.

The goal of this study (Lowe, Benfell et al. 1990) was to determine the safety of glutamine-enriched parenteral nutrition, seven normal volunteers over three 5 day study periods. Study subjects received infusions of parenteral nutrients containing increasing doses of glutamine (0, 0.285, and 0.570 g/kg body wt-1.d-1) substituted for alanine and glycine.

Safety results: The diets were all well tolerated and there were no adverse events were reported. Ammonia and glutamate, potentially toxic metabolites of glutamine, did not change significantly with glutamine enrichment. Results of mental-status examinations and continuous performance testing were normal and unchanged throughout the three periods..

Safety Conclusion(s): In this study, glutamine-enriched parenteral nutrient solutions were well tolerated with no reported signs of toxicity in normal humans.

17. Ziegler TR et al. Safety and metabolic effects of L-glutamine administration in humans. *JPEN J Parenter Enteral Nutr.* 1990 Jul-Aug;14(4 Suppl):137S-146S

The goals of this study (Ziegler, Benfell et al. 1990) were to evaluate the clinical safety, pharmacokinetics, and metabolic effects of L-glutamine in humans. Glutamine was infused intravenously in normal subjects over 4 hour at doses of 0.0125 and 0.025 g/kg/hr. Glutamine was also evaluated as a component of parenteral nutrition solutions (0.285 and 0.570 g/kg/day) administered for 5 days to 7 normal volunteer subjects and 8 bone marrow transplant patients. Measurements used to assess possible toxicity included: blood glutamine, glutamate, and other amino acids levels, serum glucose, insulin, glucagon and growth hormone; urinary creatinine, ammonia, urea and total nitrogen; standard clinical chemistry, complete blood counts, mental status, vital signs, temperature and clinical and subjective evidence of toxicity.

Safety results: Intravenous administration of glutamine was well tolerated without adverse clinical or biochemical effects. No evidence of clinical toxicity of generation of toxic metabolites (ammonia and glutamate) was reported

Safety Conclusion(s): Intravenous glutamine appeared safe in normal adult volunteers in this study.

7.7.2. Other literature reports

Two other studies of interest (Heyland, Muscedere et al. 2013, van Zanten, Sztark et al. 2014) were identified in the published literature by this reviewer separately (not captured by the search terms used for the primary FDA literature review above). The studies reported an increase in mortality among critically ill patients who received parenteral nutrition containing glutamine. These studies were conducted in critically ill, mechanically ventilated patients with severe sepsis and multi-organ failures, and included both intravenous and enteral supplementation. The findings from these studies are therefore not applicable to the patient population for whom Endari use is being sought in this application.

Clinical Review

NDA 208587

Endari® (L-glutamine)

8 Post-market Experience

As noted in Sections 2.1 and 2.6 above, L-glutamine is approved (under NDA 21,667) and marketed as NutreStore (L-glutamine powder for oral solution) for the treatment of SBS in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone approved for this indication.

The Applicant reported that from August 1, 2008 to June 10, 2016, a total of (b) (4) packets of NutreStore were distributed. The NutreStore dosage is 30 g/day for 16 weeks; which equates to 284 courses of treatment with NutreStore.

In accordance with 21 Code of Federal Regulations 314.80(c)(2), annual periodic safety update reports (PSURs) have been submitted for NutreStore since approval however, no AEs have been identified during the entire post-marketing reporting period for subjects taking NutreStore.

9 Appendices

9.1. Advisory Committee Meeting

The input of the Oncologic Drugs Advisory Committee (ODAC) was sought for this application.

The main issues with the application for which AC input was sought were:

- The impact of incomplete data and imputation methods on efficacy results
- Clinical meaningfulness of the observed effect size

The advisory committee vote was requested for the following question:

- Based on the available data presented and discussed, is the overall benefit/risk profile of L-glutamine for the treatment of sickle cell disease favorable?

The Application was discussed at the ODAC meeting was held on May 24, 2017. The committee consisted of 13 voting members.

The Applicant presented the disease background and medical need, a summary of the efficacy and safety results and the Clinical Risk- benefit summary from the Applicants perspective. FDA reviewers presented statistical review considerations and overall findings from the review of this Application.

The committee acknowledged the statistical concerns identified by FDA as well as the modest benefit of Endari demonstrated in the pivotal study, but also recognized the favorable safety profile of Endari and the huge unmet need for new treatments for SCD. After detailed discussions and deliberations, the committee voted 10 (Yes) to 3 (No) in favor of approval of Endari for the treatment of sickle cell disease.

Clinical Review

NDA 208587

Endari® (L-glutamine)

9.2. Labeling Recommendations

The following key recommendations for the Endari Prescribing Information are based on this review:

- Revise the indication statement to provide the goals of therapy and clearly identify the patient population for whom treatment with Endari is indicated.
- Revise section 6.1 of the label to include demographics of the safety population and specify the number of subjects enrolled in the phase 2 and phase 3 studies.
- Include a description of serious adverse events and deaths that occurred in patients treated with L-glutamine in the text of Section 6.1.
- Include all adverse reactions that occurred in L-glutamine treated subjects in the label regardless of causality
- Combine all abdominal pain preferred terms in a grouped term analysis and define the terms that are grouped as a footnote to the table describing adverse events in Section 6.1.
- Include the safety results from pediatric subjects studied in Study 10478 and Study GLUSCC0901 in Section 8.4.
- Include the definition of the primary endpoint- sickle cell crises in Section 14.

Clinical Review

NDA 208587

Endari® (L-glutamine)

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Clinical Review

NDA 208587

Endari® (L-glutamine)

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Clinical Review

NDA 208587

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