NDA 208587: L-glutamine

FDA Presentation

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Outline

- Introduction
  - L-glutamine: proposed indication
  - Major issues for Advisory Committee
- Clinical Studies supporting NDA
  - Study design
  - Efficacy
  - Safety
- Summary

L-glutamine

Proposed Indication:

For the treatment of sickle cell disease (SCD)

Proposed dose: 0.3 grams(g)/kilogram(kg) body weight, upper limit of 30 g/day, orally twice daily

Two Clinical Trials Conducted

Major Issues:

1. Statistical issues: Impact of incomplete data and imputation methods on efficacy results
2. Clinical meaningfulness of the trial data

Study 1: GLUSCC09-01

- Study Population:
  - Patients with Sickle Cell Anemia (SCA) or sickle β^0-thalassemia (≥5 years old)
  - 2 or more painful crises in 12 months prior to screening
- Randomized to L-glutamine versus placebo (2:1 ratio)
- Stratified by study site and hydroxyurea (HU) use
- L-glutamine dose: 0.3 g/kg body weight, orally, twice daily, (upper limit of 30 g/day)
- 4-weeks screening, 48 weeks treatment period, 3 weeks tapering, and 2 week follow-up period. Monthly study visits

Primary Endpoint
(GLUSCC09-01)

- Number of sickle cell crises (SCC) through Week 48
- SCC defined as:
  - Visit to a medical facility for SCD-related pain; treated with a parenterally administered narcotic or toradol; or
  - Acute chest syndrome (ACS), priapism, and splenic sequestration
- SCC adjudicated by Central Adjudication Committee (CAC)

Secondary Endpoints
(GLUSCC09-01)

- Number of sickle cell crises at Week 24
- Number of hospitalizations for sickle cell pain
- Number of ER visits for sickle cell pain
- Hematological parameters

Demographics
(GLUSCC09-01, N=230)

- Age: Mean 22 years; Range: 5-58 years
- Race/ethnicity: 94% Black, 3% Hispanic, 3% Other
- Gender: 54% Female
- Diagnosis: 90% Sickle cell anemia

  9% - Sickle β^0 thalassemia

  1% - Sickle β^+ thalassemia
- Hydroxyurea (HU) use at baseline: 67%

Subject Disposition (GLUSCC09-01)

	L-Glutamine n=151	Placebo N=78	Total N=229
Completed Study	64%	76%	68%
Discontinued study*	36%	24%	32%
Reason for discontinuation			
Consent Withdrawn	15%	11%	14%
Non compliance	5%	1%	4%
Loss to follow-up	3%	4%	3%
Adverse events	3%	0%	2%
Deaths	1%	0%	1%
Other	8%	8%	8%

*Discontinued before Week 48

Study 2: 10478

Study design similar to GLUSCC09-01. Except:

- Randomization 1:1 ratio
- Stratified by study site but not by HU use
- HU use not balanced between treatment arms at baseline

Primary Endpoint - Study 10478

- Number of SCC through Week 48
- SCC defined as:
  - Visit to a medical facility that lasted > 4 hours for acute sickling-related pain; treated with a parenterally administered narcotic
  - ACS, priapism, hepatic and splenic sequestration
- SCC not adjudicated by CAC

Subject Disposition (Study 10478)

	L-glutamine N=37	Placebo N=33	Total N=70
Completed Study	49%	36%	43%
Discontinued study*	51%	64%	57%
Reason for discontinuation			
Non compliance	24%	27%	26%
Consent Withdrawn	8%	15%	11%
Lack of efficacy	0%	3%	1%
Loss to follow-up	5%	3%	4%
Adverse events	0%	3%	1%
Deaths	3%	0%	1%
Other	11%	12%	11%

*Discontinued before Week 48

FDA Analysis

- Efficacy:
  - Study GLUSCC09-01

- Safety:
  - Study GLUSCC09-01
  - Study10478

NDA 208,587
Oral L-glutamine For Patients With Sickle Cell Disease
Statistical Review Considerations

May 24, 2017

Oncologic Drugs Advisory Committee

Che Smith, PhD – Statistical Reviewer
Yuan Li Shen, DrPH – Team Leader, Statistics
Thomas Gwise, PhD – Deputy Division Director, Statistics

STUDY 10478
STATISTICAL ISSUES

- Different definition of a sickle cell crisis
- Un-adjudicated primary efficacy endpoint
- Early study dropout
- Primary efficacy result did not meet level of significance
  - Potential misconduct at one study site
  - Heterogeneous study population across treatment arms

STUDY GLUSCC09-01
STATISTICAL ISSUES

- High early dropout rate and differential dropout rates between treatment arms
- Imputation of incomplete sickle cell crisis event counts
- Interpretation of efficacy results based on data impacted by dropouts

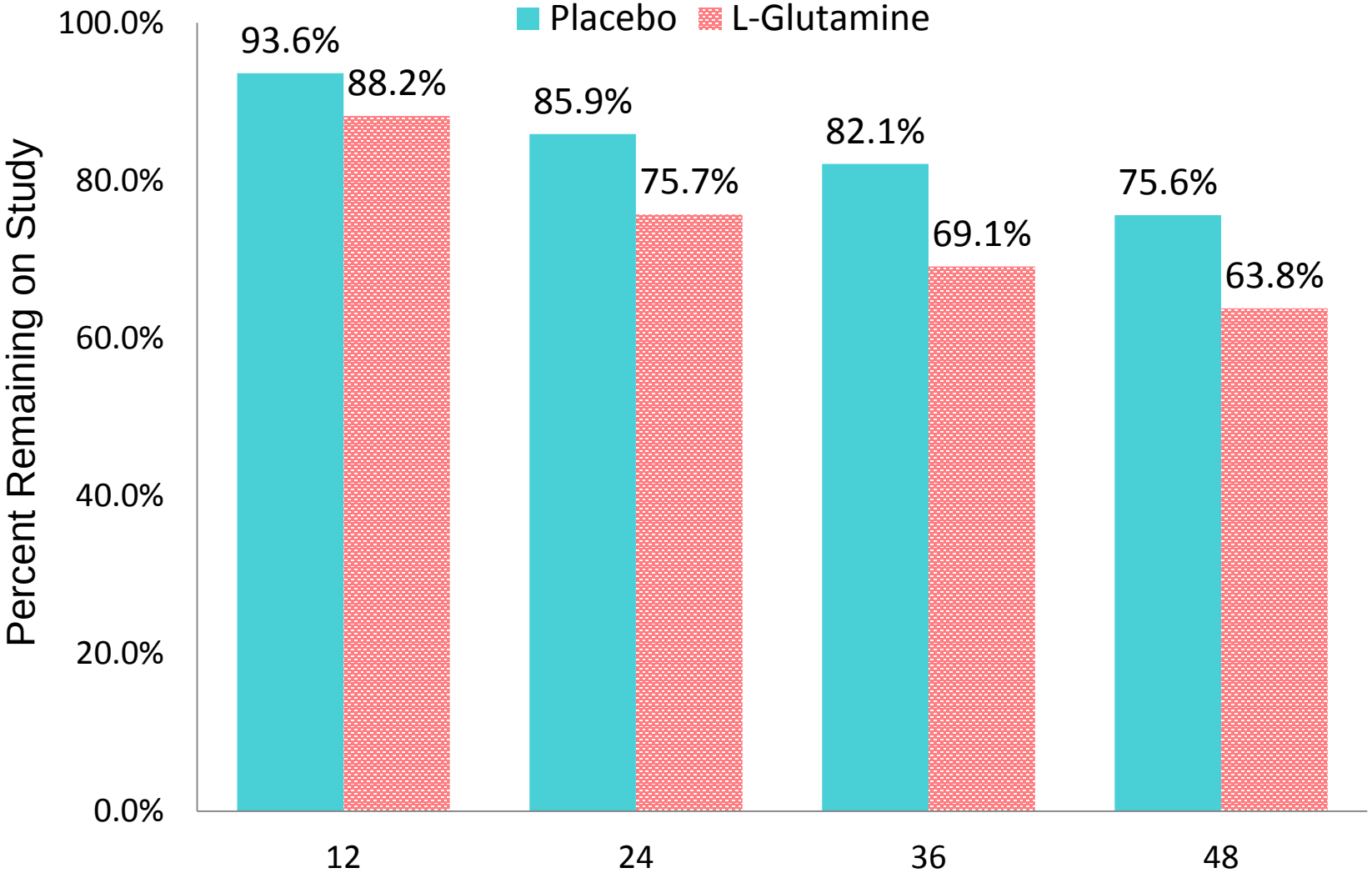
Study 0901 Overview

- Randomized, placebo-controlled, multicenter study
- Enrolled 230 patients with SCA or sickle β^0-thalassemia, ≥ 5 years of age, with 2+ painful crises in previous 12 months
- Randomized 2:1 to L-glutamine or placebo treatment, respectively; stratified by site and baseline HU use
- 48 week treatment period, 3 week taper, 2 week follow up
- Primary Efficacy Endpoint: number of sickle cell crises
- Secondary Efficacy Endpoints: SCC at 24 weeks, hospitalizations, emergency room visits, hematologic parameters

Statistical Analysis Plan

	Study GLUSCC09-01
Sample size specification	Based on Wilcoxon Rank Sum Test Significance level: 0.045 80% power to detect difference in distributions of the number of sickle cell crises at Week 48
Pre-specified primary efficacy analysis	Number of sickle cell crises (SCC) at Week 48, CMH test using Modified Ridit scores
Stratification Factors	Study center region Hydroxyurea use at baseline
Secondary efficacy endpoints	Number of SCC at 24 weeks Number of hospital visits Number of ER visits Hematological parameters
Interim Analysis	Number of SCC at 24 weeks 0.005 significance level
Post hoc sensitivity analyses	Negative Binomial regression Removing one or both stratification factor(s) Time-adjusted/ last observation carried forward

Study Dropout Over Time By Treatment Group



SOURCE: FDA Analysis

Patient Experiences on Study GLUSCC09-01

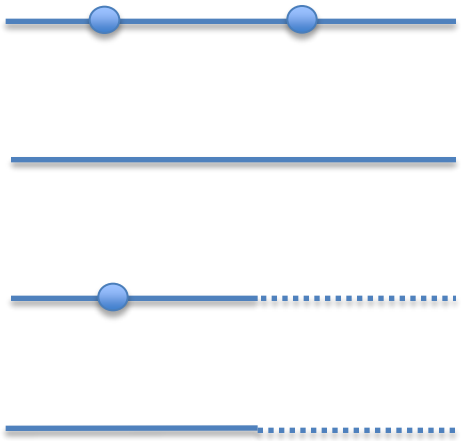
Completed 48 weeks of treatment; at least one crisis recorded

Completed 48 weeks of treatment; no crises were recorded

Dropped out before week 48; at least one crisis recorded

Dropped out before week 48; no crises recorded

Patient Experiences on Study GLUSCC09-01



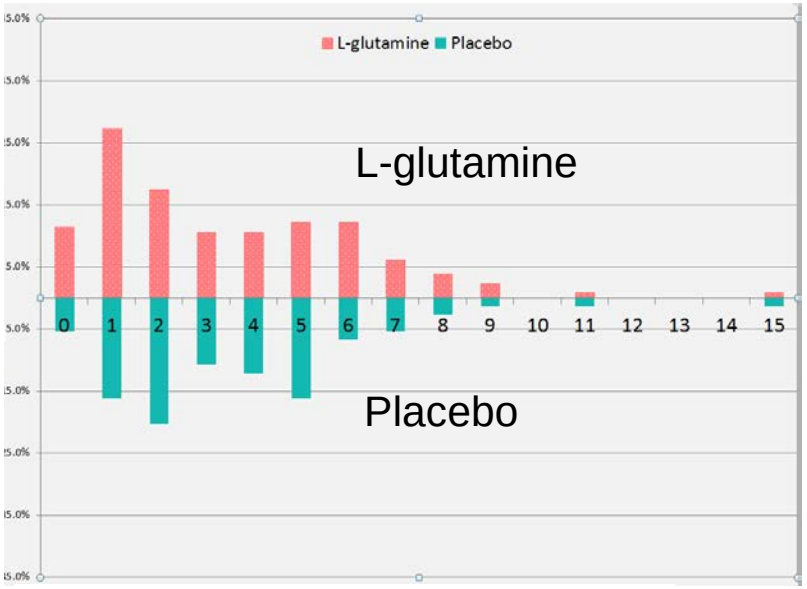
Subset	L-glutamine N = 152	Placebo N = 78
48 week completers; at least one SCC	82 (53.9%)	55 (70.5%)
48 week completers; no recorded SCC	15 (9.9%)	4 (5.1%)
Dropped out; at least one SCC	35 (23.0%)	15 (19.2%)
Dropped out; no recorded SCC	20 (13.2%)	4 (5.1%)
Total	**152**	**78**

SOURCE: FDA Reviewer analysis

Comparing Distributions Of The Number Of Sickle Cell Crises By Treatment Group

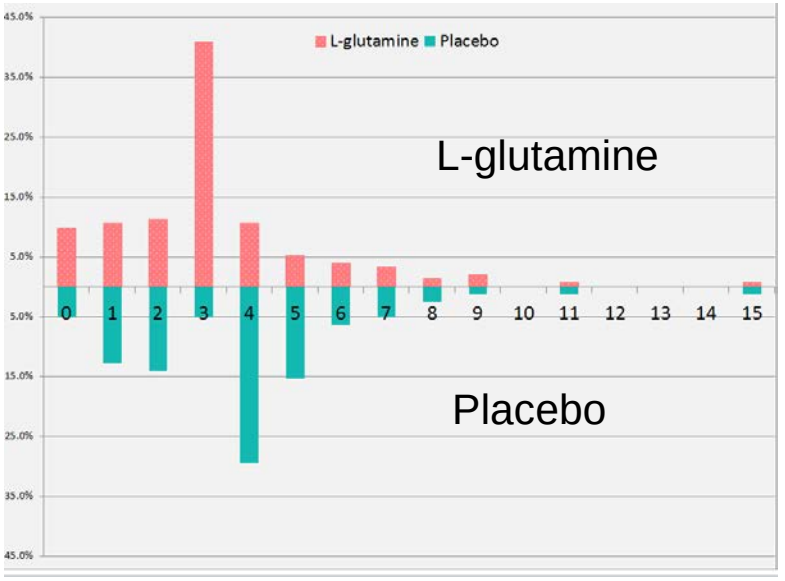
Histograms of observed data, and observed data with Applicant's imputation

Reported SCC counts



Number of sickle cell crises

Reported SCC counts after imputation



Number of sickle cell crises

Applicant's imputation rule:
max(crises experienced up to dropout, mean crises among completers in treatment group)

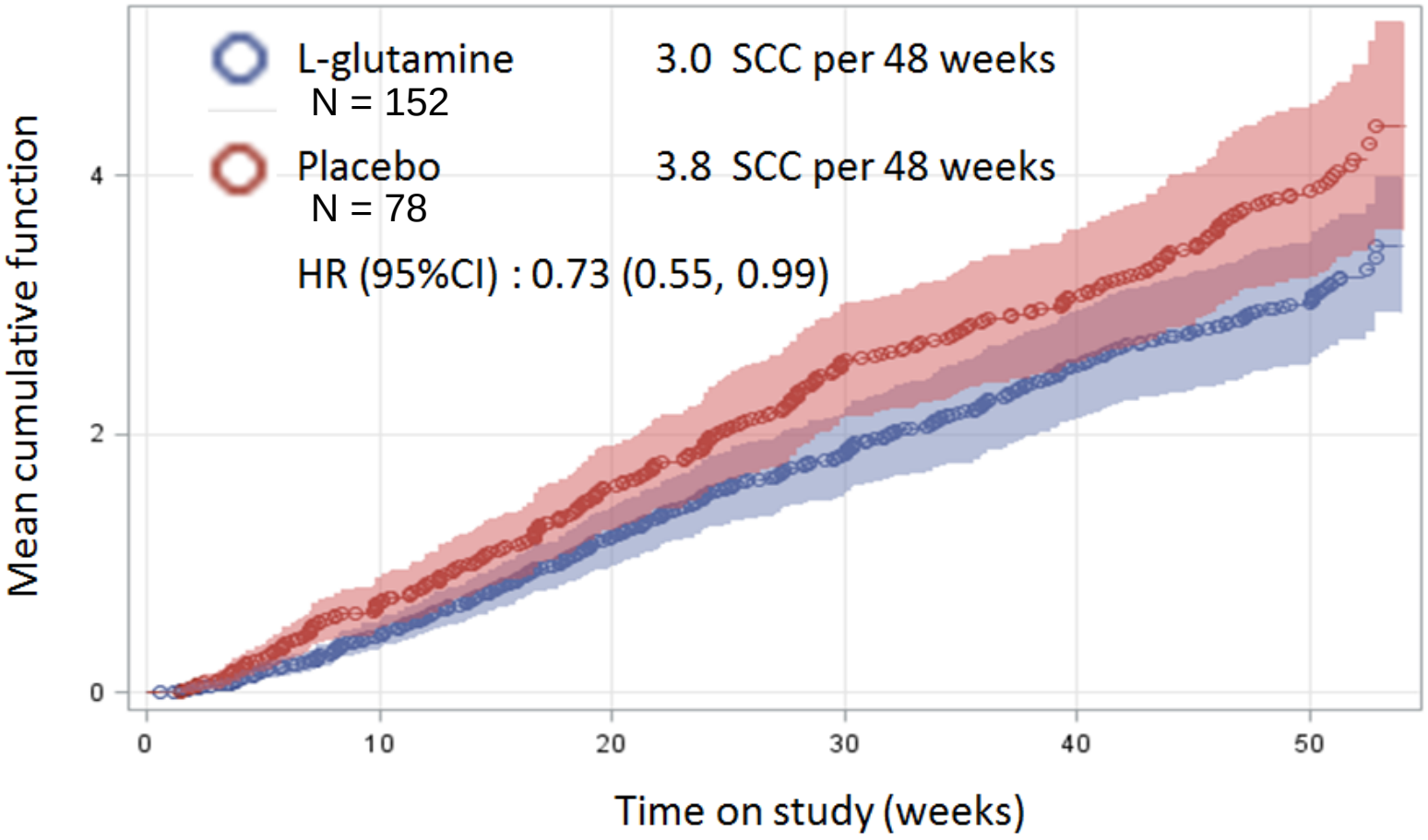
SOURCE: Applicant's Integrated Summary of Efficacy, Table 1.2; FDA Reviewer analysis

Applicant's Efficacy Results

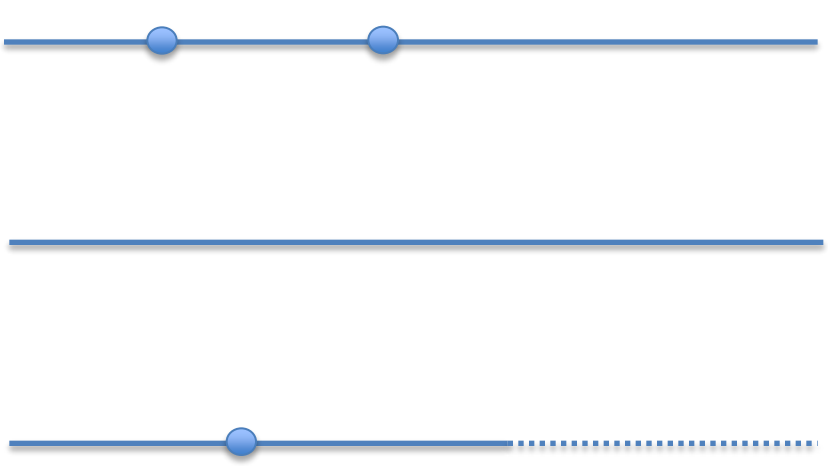
Primary Efficacy Analysis	L-glutamine (N = 152)	Placebo (N = 78)	p-value
Median number of sickle cell crisis events at 48 weeks (min, max)	3 (0, 15)	4 (0, 15)	0.0052
Secondary Efficacy Analysis	**L-glutamine (N = 152)**	**Placebo (N = 78)**	**Nominal p-value**
Median number of sickle cell crisis events at 24 weeks (min, max)	2 (0, 8)	2 (0, 7)	0.179
Median number of hospitalizations at 48 weeks (min, max)	2 (0, 14)	3 (0, 13)	0.041
Median number of emergency room visits at 48 weeks (min, max)	1 (0, 12)	1 (0, 15)	0.128

SOURCE: Applicant's Integrated Summary of Efficacy, Table 14; Applicant's Study GLUSCC09-01 Study Report
All analyses adjusted for region and baseline hydroxyurea use;
CMH = Cochran-Mantel-Haenzsel; CMH test using modified ridit scores

FDA Analysis: Proportional Rate Of Sickle Cell Crisis Events By Treatment Group



Patient Experiences on Study GLUSCC09-01



Completed 48 weeks of treatment; at least one crisis recorded

Completed 48 weeks of treatment; no crises were recorded

Dropped out before week 48; at least one crisis recorded

FDA Sensitivity Analysis Population
N = 206

FDA Exploratory Analyses Comparing Rates Of Sickle Cell Crisis Events Per 48 Weeks Using Negative Binomial Regression

FDA strategy for handling incomplete crisis counts	Rate of crises/48 weeks L-glutamine vs Placebo	Rate Ratio [95% CI] Based on Negative Binomial model
FDA sensitivity analysis population N=206	3.3 v 4.1	0.80 [0.64, 1.01]
ITT population, assuming incomplete crisis counts for 24 patients are "0", N=230	3.3 v 4.2	0.77 [0.61, 0.99]
Multiple Imputation (FCS)* for 24 patients with incomplete crisis counts, N=230	3.9 v 4.3	0.91 [0.73, 1.12]

SOURCE: FDA Reviewer analysis
All analyses adjusted for region and baseline hydroxyurea use; using time on study as offset
*FCS = fully conditional specification;
The multiple imputation approach adjusts for treatment group study site, baseline hydroxyurea use, age, baseline crisis count, and time spent on study to impute crisis counts for 24 patients.

Summary

- FDA explored alternative imputation and analytic methods to assess the impact of study dropout
- An FDA analysis estimated cumulative rates of crises at week 48:
  - 3.0 vs. 3.8 for L-glutamine vs. Placebo
    [HR: 0.73, 95%CI: (0.55, 0.99)]
- All other exploratory analyses show a trend in favor of L-glutamine to reduce the number of SCC over 48 weeks; this trend should be considered in the context of the product's safety profile

SAFETY

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SAFETY OVERVIEW

- No major safety issues
- Review findings:
  - Overall, similar pattern and frequency of common TEAEs and TEAEs that led to study withdrawal between treatment groups
  - Lower frequency of SAE reports of SCA with crisis and ACS among L-glutamine treated patients supports efficacy findings

Safety Population

- Integrated safety database:
  - All subjects from Studies 10478 and GLUSCC09-01 who received ≥ 1 dose of study medication

- Data from studies 8288, 8822, 8775, 10779 and 10511 not included in integrated safety review
  - Early stage, different methodologies
  - Adverse events not as explicitly defined

Summary of Drug Exposure (Safety Population, N= 298)

- 187 subjects received L-glutamine for ≥ 1 day
  - 73% treated for ≥ 24 weeks,
  - 58% treated for ≥ 48 weeks
- Total exposure
  - L-glutamine = 138 subject-years
  - Placebo = 86 subject years

Summary of Adverse Events (Safety Population)

Subjects with at least 1:	L-glutamine N = 187	Placebo N = 111
TEAE*	96%	97%
Drug-related TEAE	19%	13%
SAE**	75%	80%
Drug-related SAE	2%	3%
Deaths (all)	2%	0%
TE*** Deaths	2%	0%
Deaths due to drug-related TEAEs	0%	0%

*TEAE = treatment emergent adverse event; **SAE = serious adverse event

***TE = Treatment emergent

Treatment Emergent Deaths

- Three treatment emergent deaths
  - Patients aged 37, 45, and 46 years
  - All occurred > 300 days on study GLUSCC09-01
- Cause of death
  - cardiac arrest; respiratory failure, sickle cell crisis; severe anemia; severe hypoglycemia
- None considered treatment related. No autopsies done
- Insufficient information for causality assessment

Serious Adverse Events* (Safety Population)

	L-glutamine (n=187)	Placebo (n- 111)
SCA§ with crisis	66%	72%
Acute chest syndrome	7%	19%
Pneumonia	5%	9%
Chest pain	3%	2%
Pyrexia	3%	4%
Asthma	3%	3%

*Occurring in ≥ 2% of L-glutamine-treated subjects
§SCA = Sickle cell anemia

Common Adverse Events (≥10%) in L-glutamine patients:

Constipation (21%), nausea (19%), headache (18%), pyrexia (17%), abdominal pain (16%) cough (15%), URTI* (14%), pain in an extremity (13%), vomiting (13%), back pain (12%), chest pain (12%) and arthralgia (12%)

*URTI = Upper respiratory tract infection

No notable differences in TEAEs or SAEs by demographic variables

No notable differences in changes in hematology parameters, liver function test or serum chemistry between treatment groups

SUMMARY

Efficacy Summary

- Primary efficacy analysis for Study GLUSCC09-01
  - Applicant: Median SCC counts at 48 weeks of 3 vs 4 for L-glutamine vs placebo (p = 0.0052)
  - FDA: Estimated mean cumulative rates of SCC at 48 weeks of 3 vs 3.8 for L-glutamine vs placebo [HR: 0.73, 95% CI: (0.55, 0.99)]
- No ideal analytic method given magnitude of drop-outs and imputations

Safety Summary

- Overall, similar frequency of TEAEs or TEAEs that led to study drug withdrawal among L-glutamine and placebo treatment groups
- Lower frequency of SAEs (SCA with crisis, ACS) among L-glutamine treated subjects suggests benefit
- Common Adverse events:
  - constipation, nausea, headache, pyrexia, abdominal pain, cough, URTI, pain in an extremity, vomiting, back pain, chest pain and arthralgia

Major Issues for the ODAC

- **Discuss**:
  - The impact of study drop-out rates, data imputation and analytic methods on interpretation of efficacy findings
  - Clinical significance of one fewer median sickle cell crises/year in patients with SCD

Question for ODAC

- **Vote:**
  - 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?