GMI-1070: Reduction in Time to Resolution of Vaso-Occlusive Crisis and Decreased Opioid Use in a Prospective, Randomized, Multi-Center Double Blind, Adaptive Phase 2 Study In Sickle Cell Disease (GMI-1070-201)

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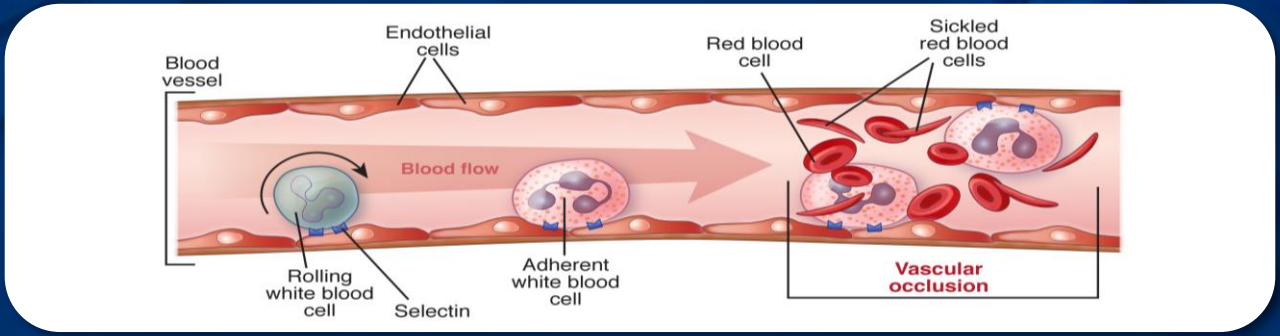
Vaso-Occlusion in Sickle Cell Disease

- Acute vaso-occlusive crisis (VOC)
  - Most common disease manifestation in sickle cell disease (SCD)
  - Accounts for more than 75,000 hospitalizations/year in the US [1]
- Hydroxyurea (HU), the only drug approved for SCD, decreases the frequency of but does not eliminate VOC.[2]

[1] Davis H et al, Public Health Rep 1997
[2] Charache et al, NEJM 1995

Role of Selectins and Selectin Inhibition

- Animal models support a role for selectin-mediated adhesion in VOC
  - Adherent and activated leukocytes, as well as SS RBCs, contribute to the vaso-occlusive process by binding to E- and P-selectins on endothelial cells.
  - Vaso-occlusion is inhibited in mice deficient in P- and E-selectins (Turhan et al, PNAS 2002)
- GMI-1070 is a novel small molecule inhibitor of E-, P-, and L-selectins
  - Preclinical models demonstrated efficacy in reducing cell adhesion and abrogating VOC.



GMI-1070

- When used in a SCD animal model in which VOC was established before attempting treatment, GMI-1070 demonstrated several positive effects (Chang et al. Blood 2010):
  - Increased survival
  - Improved blood flow
  - Reduced leukocyte / endothelial interactions
  - Reduced leukocyte / SS RBC interactions
- Phase 1 studies supported the safety of GMI-1070 in both normal subjects and those with SCD.

Phase 2 Study Design

- Prospective multicenter, randomized, placebo-controlled, double-blind, adaptive study of 76 adult and pediatric SCD patients
  - Subjects enrolled at the time of admission to the hospital
  - GMI-1070 or placebo given in addition to standard care for VOC
  - Interim analyses for PK and safety were built in
- Primary endpoint – Time to Resolution of VOC
  - Composite endpoint, analyzed as 'time to event' for the first component achieved
    - *Sustained reduction of ≥1.5 cm **and** transition to oral analgesics*
    - *Readiness for discharge*
    - *Time to discharge*
- Secondary endpoints
  - Additional efficacy components – length of hospital stay, opioid utilization
  - Safety profile – including rate of SCD-related complications (e.g. acute chest syndrome, transfusion, rehospitalization)
  - Pharmacokinetics (PK)

Analysis

- Statistical methods:
  - Comparisons: GMI-1070 vs. placebo
  - Efficacy outcomes were evaluated by:
    - Analysis of covariance (ANCOVA) adjusting for sex and age
    - Kaplan-Meier analysis (using log rank test)
  - Secondary outcomes were evaluated by:
    - Mixed analysis of covariance model adjusting for sex and age
    - Fisher's exact test

Inclusion and Exclusion Criteria

Inclusion

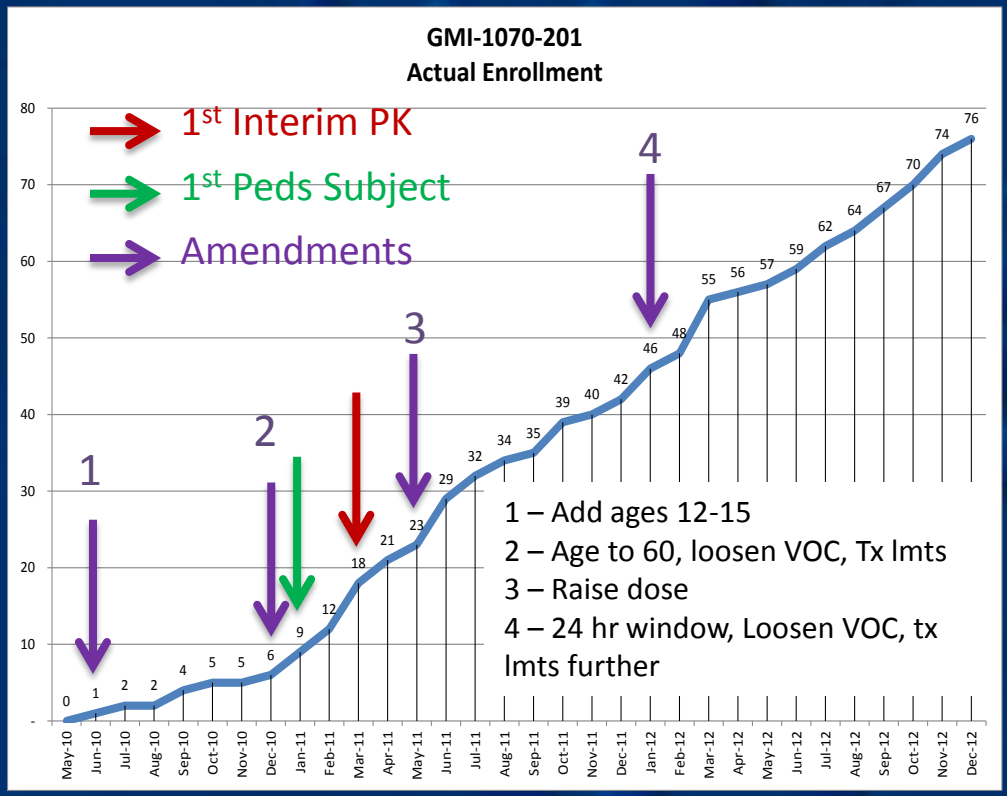
- Confirmed diagnosis of HbSS or HbS-β^0thal
- Diagnosis of VOC, hospitalized or being admitted
- Able to dose within stipulated hours of first medical evaluation for VOC (not including triage)
- 16–45 years old initially, extended to 12-60

Exclusion

- Serious infection
- Acute chest syndrome
- Pain atypical of VOC
- Serum creatinine >1.2 mg/dL (adults) or >1.0 mg/dL (age <16)
- Greater than stipulated number of hospitalizations for VOC
- Recent transfusion of pRBCs

Study Conduct and Enrollment

- Drug dose was doubled after 1st interim PK
- Final Enrollment
  - 76 patients dosed
    - 56 adult, 20 pediatric
  - 45 enrolled at the higher dose regimen
    - 35 adult, 10 pediatric
  - 17 sites enrolled
    - 22 sites in total participated in study
- Total enrollment period – 31 months (2010-2012)

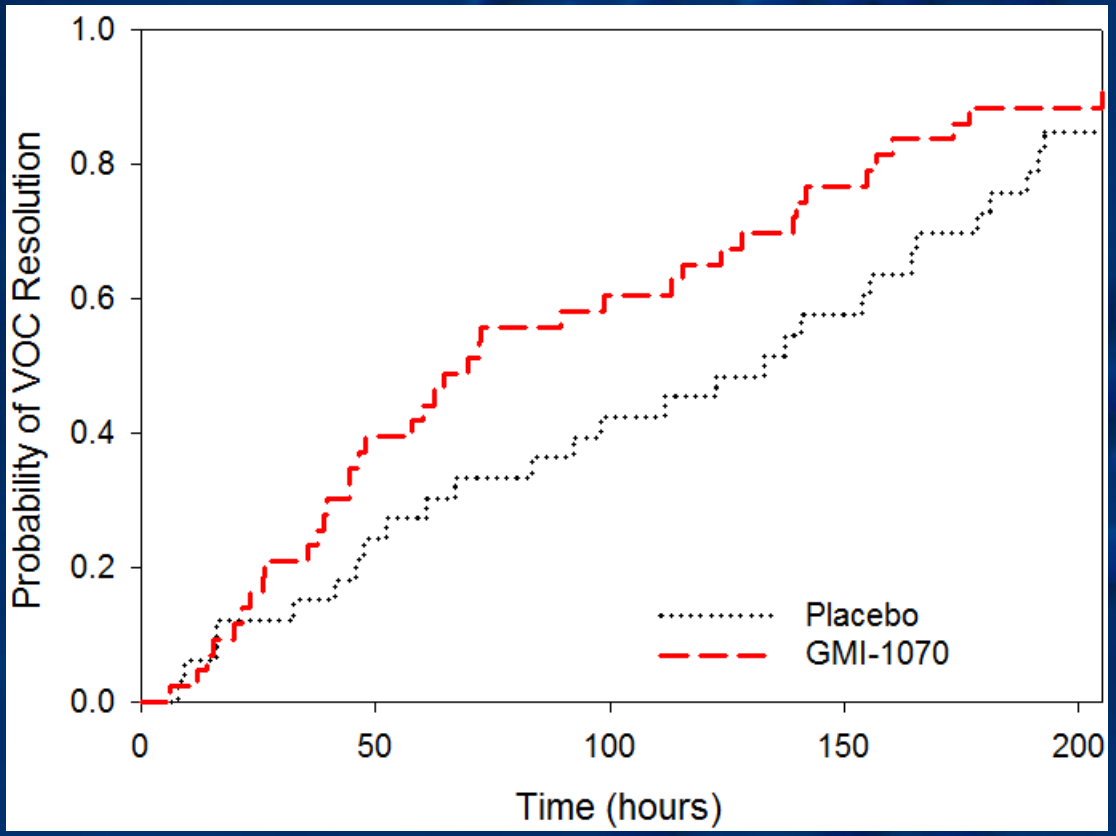


Baseline Subject Characteristics

		GMI-1070	Placebo
Age (years), Mean (SD)		25.4 (10.8)	25.0 (10.2)
Gender N (%)	**Male**	18 (41.9)	13 (39.4)
Genotypes	**HbSS**	39	30
	Hb S^0 thalassemia	1	3
	HbSC	3	0
Hydroxyurea therapy, N (%)		22 (51.2%)	23 (69.7%)
Daily out-patient pain meds, N (%)		18 (41.9%)	19 (57.6%)
≥3 VOC admissions in previous 12 months, N (%)		13 (30.2%)	14 (42.4%)
ACS in previous 12 months, N (%)		5 (11.6%)	6 (18.2%)
VAS at presentation, mean (SD)		8.3 (1.6)	9.0 (1.5)
Hemoglobin g/dL, mean (SD)		8.3 (1.4)	8.2 (2.1)
WBC x 10^3, mean (SD)		12.8 (5.0)	13.6 (5.6)
ANC x10^3/ml, mean (SD)		7.3 (3.9)	8.3 (5.1)

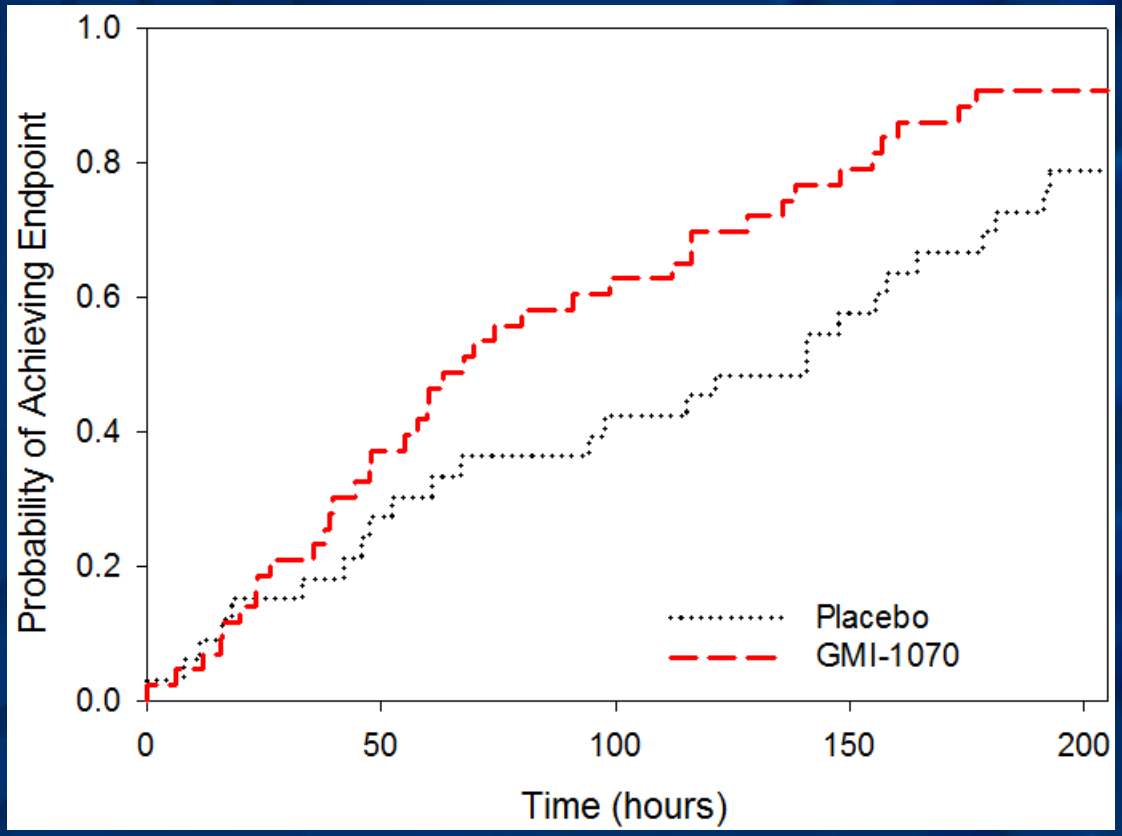
Time to Resolution of VOC

- Resolution of VOC was defined as the first of the following to occur:
  - Sustained decrease in pain score of at least 1.5 cm out of 10 cm since baseline, AND transition to oral pain medications per hospital procedures;
  - OR readiness for discharge as stated by the physician and subject;
  - OR discharge to home setting



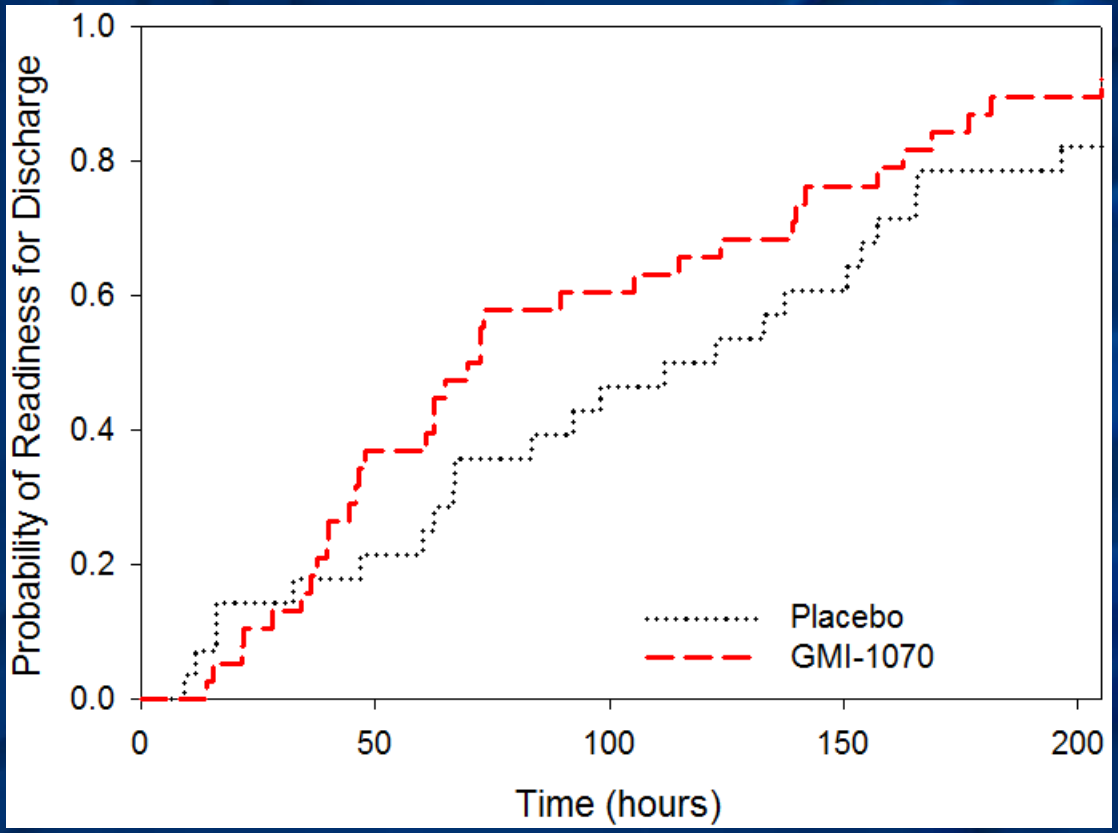
	GMI-1070	Placebo	Reduction	P
LS Mean, h ± SE	103.6 ± 20.9	144.6 ± 23.5	28%	0.19
Median, h (CI)	69.6 (44.3, 115.5)	132.9 (67.0, 164.2)	48%	0.19

Combined Pain Response and Transition to Oral Analgesics



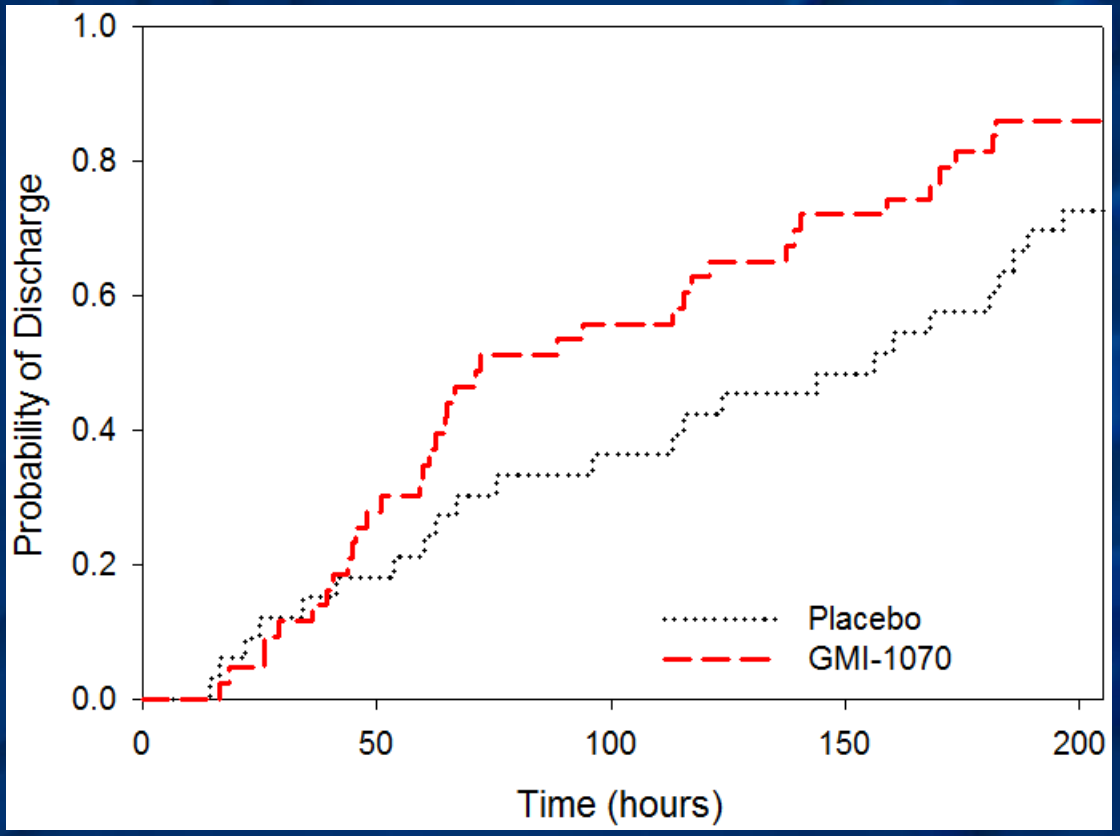
	GMI-1070	Placebo	Reduction	P
LS Mean, h ± SE	87.8 (15.9)	135.2 (17.5)	35%	0.05
Median, h (CI)	128.0 (57.7, 156.9)	181.0 (97.7, 217.0)	29%	0.20

Agreement about Discharge Readiness



	GMI-1070	Placebo	Reduction	P
LS Mean, h ± SE	97.6 ± 16.6	133.1 ± 19.5	27%	0.17
Median, h (CI)	72.5 (60.9, 139.1)	137.4 (83.2, 165.7)	47%	0.15

Time to Discharge



	GMI-1070	Placebo	Reduction	P
LS Mean, h ± SE	118.8 ± 21.7	173.5 ± 24.5	32%	0.10
Median, h (CI)	72.2 (59.9, 121.0)	156.1 (75.4, 185.8)	54%	0.09

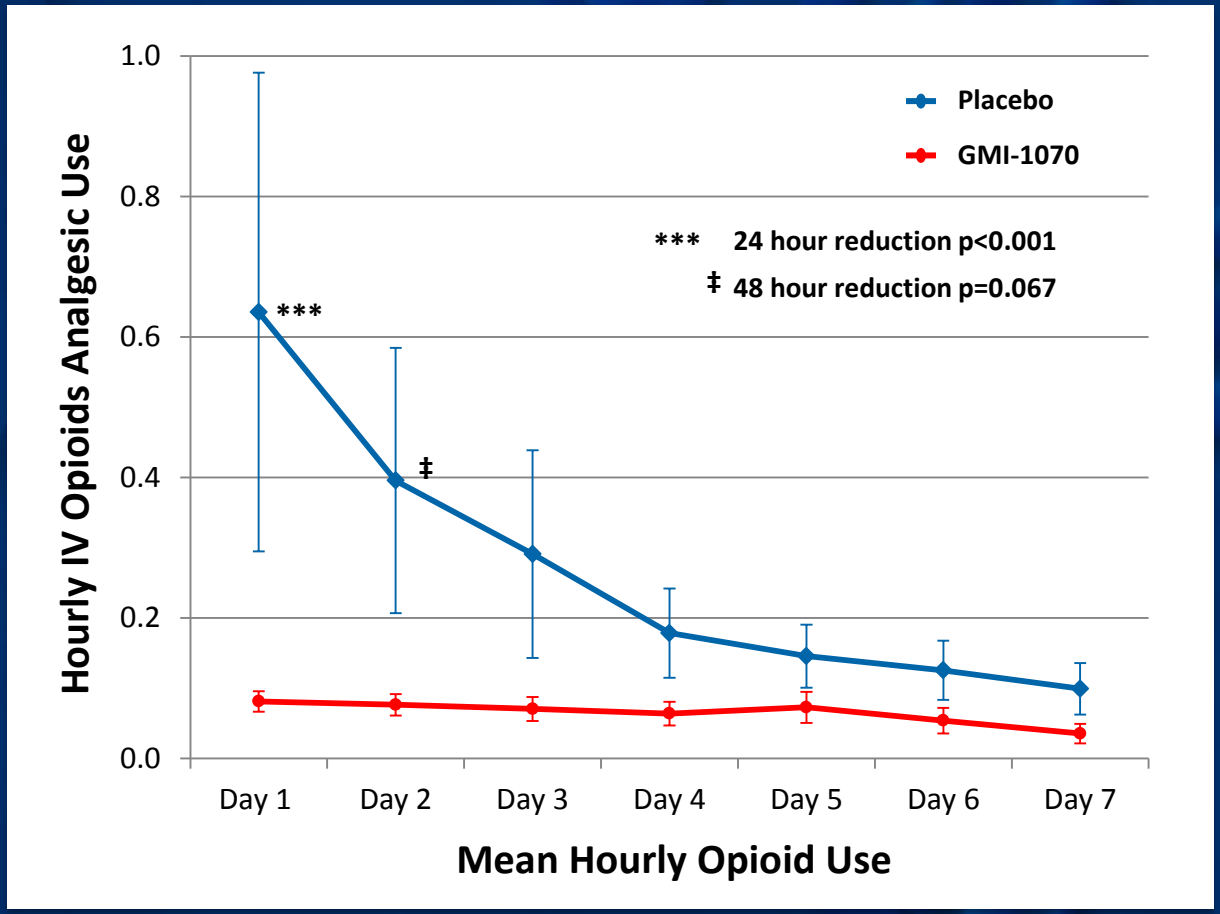
Resolution of VOC and Length of Stay

	GMI-1070	Placebo
Resolution of VOC Achieved at Various Time Points Cumulative (%)	N = 43	N = 33
48h	39.5%	24.2%
72h	51.2%	33.3%
96h	58.1%	39.4%
120h	65.1%	45.5%
Hospital Length of Stay (h)		
LS Mean ± SE	131.65 (21.5)	182.1 (24.6)
Median (CI)	84.8 (66.1, 132.4)	165.1 (79.6, 187.8)

Significant Reduction in Opioid Use

Cumulative IV opioids:

- **Mean reduced by 83% (p=0.010)**
- **Median reduced by 69% (p=0.056)**



SCD-Related and Treatment Emergent AEs

SCD-Related AEs						
Treatment Group	**Acute Chest Syndrome N (%)**	**RBC Transfusion N (%)**	**ICU Stay N (%)**	**Death**	**Readmission for VOC (14 days)**	**Readmission for VOC (30 days)**
GMI-1070 N=43	6 (14.0%)	15 (34.9%)	0	0	4 (9.3%)	9 (20.9%)
Placebo N=33	3 (9.1%)	17 (51.5%)	1 (3%)	0	3 (9.1%)	7 (21.2%)
Treatment Emergent AEs						
	Gastrointestinal Disorders	**Rash**	**Hepatobiliary**	**Renal/ Urinary**	**Pyrexia**	**Headache**
GMI-1070 N=43	18 (41.9%)	6 (14.0%)*	2 (4.7%)	3 (7.0%)	8 (18.6%)	8 (18.6%)
Placebo N=33	12 (36.4%)	2 (6.1%)	2 (6.1%)	2 (6.1%)	6 (18.2%)	4 (12.1%)

*One patient developed acute generalized exanthematous pustulosis after discharge; this resolved without intervention.

Conclusions

- Use of GMI-1070 during VOC improved multiple outcomes:
  - Time to resolution
  - Length of hospital stay
  - Requirement for parenteral opioid analgesia
- Improvements were seen in every efficacy endpoint explored and across every subgroup evaluated.
- In some cases, improvements achieved statistical significance even in this small population with high variability.
- GMI-1070 had a benign safety profile in this trial.
- These results support study of GMI-1070 for efficacy for treatment of VOC in a phase 3 clinical trial.

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