

(S263) THE SAFETY, PHARMACOKINETICS & PHARMACODYNAMIC EFFECTS OF IMR-687, A HIGHLY-SELECTIVE PDE9 INHIBITOR, IN ADULTS WITH SICKLE CELL DISEASE: PHASE-2A PLACEBO-CONTROLLED & OPEN LABEL EXTENSION STUDIES

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Session S432: Changing the scene on sickle cell disease

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VIRTUAL

DISCLOSURES

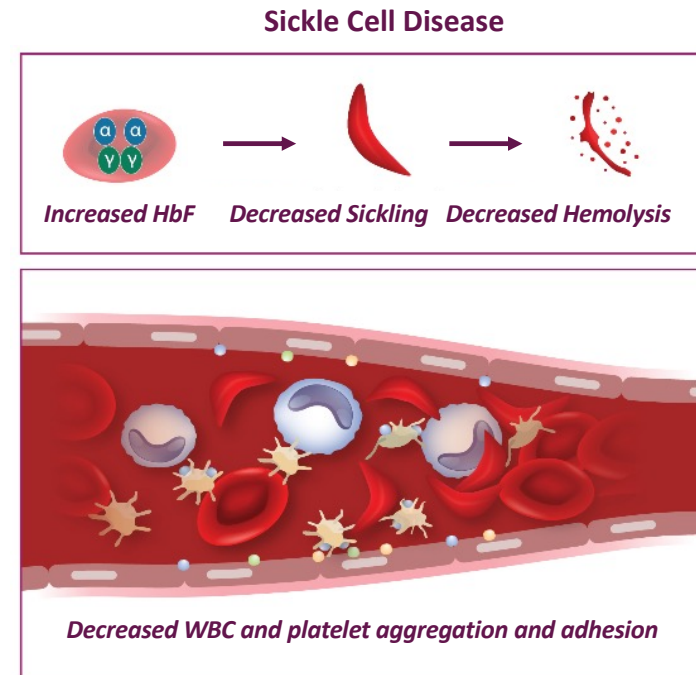
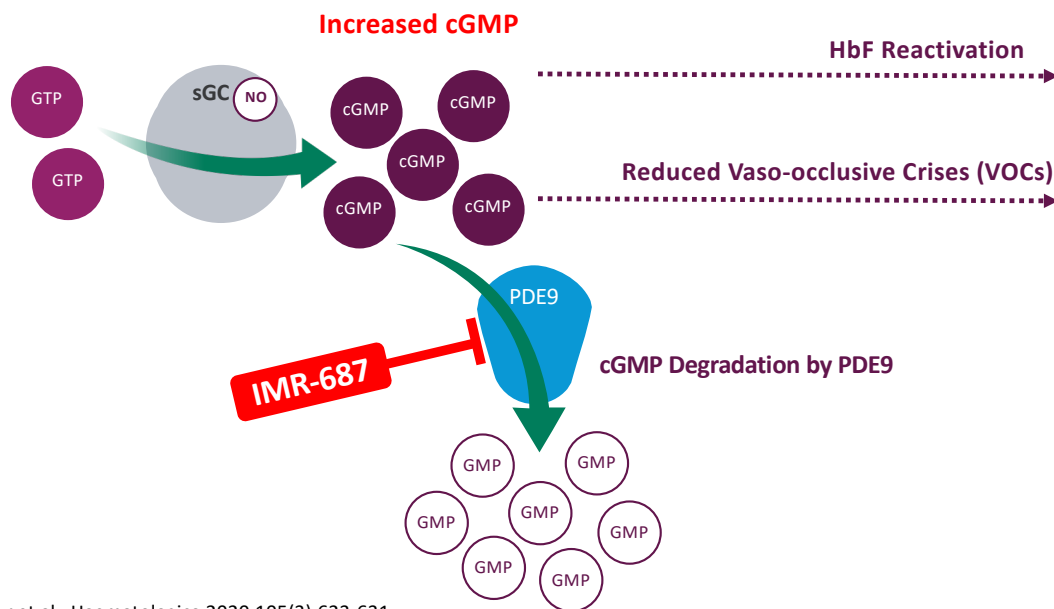
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Overview: IMR-687 Multimodal Mechanism of Action in SCD

- IMR-687 is a novel, orally-administered, small molecule, highly selective inhibitor of phosphodiesterase-9 (PDE9) being investigated for the treatment of sickle cell disease (SCD) and β -thalassemia
 - Inhibition of PDE9 results in increased cGMP, which can lead to increased HbF and reduced adhesion molecules



IMR-687: Phase 2a Studies in Adults with SCD

Parent Study

(N=93, study completed)

- 6-month* randomized, double-blind, placebo-controlled study, ± background hydroxyurea (HU)
- IMR-687 oral, once daily, dose escalation after 1–3 months
- **Primary objective:** Safety and tolerability
- **Secondary & exploratory objectives:** PK profile, PD biomarkers, VOCs, patient-reported outcomes

IMR-687 Monotherapy, N=58

Combo IMR-687 + HU, N=35

| N | Parent Study | |
|----|--------------|---------|
| | 20 | Placebo |
| 12 | 50mg | 100mg |
| 26 | 100mg | 200mg |
| 10 | Placebo | |
| 25 | 50mg | 100mg |

Rollover with (N=17) or without (N=7) treatment interruption

OLE Study

(N=24, study ongoing)

- N=17 subjects on monotherapy IMR-687
- N=7 subjects on combination IMR-687 + HU
- 4-year safety study
- Data presented as of 12May2021 (labs as of 29Apr2021)

Mono/Combo IMR-687±HU, N=24

Open-Label Extension (OLE) Study

200mg

*In the monotherapy cohorts, all subjects were treated for up to 6 months

In the combination cohorts, 21 subjects were treated for up to 4 months, and 14 subjects were treated for up to 6 months

Parent Study: Baseline Demographics & Disease Characteristics

| | IMR-687/Placebo, Monotherapy | | | IMR-687 + HU/Placebo + HU | |
|---|------------------------------|---------------------|----------------------|---------------------------|---------------------|
| | Placebo (N=20) | 50/100 mg (N=12) | 100/200 mg (N=26) | Placebo (N=10) | 50/100 mg (N=25) |
| Age (yr), median, range | 34.5 (20, 50) | 34 (19, 50) | 29 (18, 51) | 29 (19, 42) | 30 (18, 51) |
| Gender, n (male/female) | 8 / 12 | 4 / 8 | 9 / 17 | 1 / 9 | 10 / 15 |
| Race, n (black/other or missing) | 19 / 1 | 12 / 0 | 25 / 1 | 9 / 1 | 24 / 1 |
| Genotype, n (%) | | | | | |
| Homozygous HbSS | 18 (90.0) | 12 (100) | 23 (88.5) | 10 (100) | 23 (92.0) |
| Sickle- β^0 Thalassemia | 1 (5.0) | 0 | 2 (7.7) | 0 | 0 |
| Missing | 1 (5.0) | 0 | 1 (3.8) | 0 | 2 (8.0) |
| Baseline HbF [%], Mean (SD) | 5.1 (3.74) n=19 | 13.9 (7.65) | 9.5 (6.81) n=25 | 14.6 (7.68) N=9 | 15.6 (8.28) N=24 |
| Hospitalizations for VOC in Prior Year, n (%) | | | | | |
| None | 11 (55.0) | 7 (58.3) | 14 (53.9) | 7 (70.0) | 11 (44.0) |
| 1 | 4 (20.0) | 1 (8.3) | 7 (26.9) | 0 | 7 (28.0) |
| 2 | 3 (15.0) | 1 (8.3) | 3 (11.5) | 2 (20.0) | 1 (4.0) |
| 3 | 2 (10.0) | 2 (16.7) | 1 (3.8) | 0 | 4 (16.0) |
| 4 | 0 | 0 | 1 (3.8) | 0 | 2 (8.0) |
| Missing | 0 | 1 (8.3) | 0 | 1 (10.0) | 0 |

VOC = vaso-occlusive crisis

Parent and OLE Studies: Safety Summary

IMR-687 was well-tolerated as a monotherapy and in combination with HU

- No treatment-related serious adverse events (SAEs) or treatment-related Grade \geq 3 adverse events (AEs) in IMR-687 groups
- No clinically significant changes in laboratory safety data, ECG, or vital signs; no cases of neutropenia
- In parent study, AEs leading to treatment discontinuation occurred in N=3/30 (10%) on placebo, N=5/63 (8%) on IMR-687

Adverse Events Reported in \geq 20% subjects in any IMR-687 Group, n (%)

| | Parent Study | | | | | OLE Study |
|---|------------------------------|-----------------------------------|------------------------------------|---------------------------|-----------------------------------|-----------------------------|
| | IMR-687/Placebo, Monotherapy | | | IMR-687 + HU/Placebo + HU | | IMR-687 \pm HU |
| | Placebo (N=20) | IMR-687 50 mg/100 mg (N=12) | IMR-687 100 mg/200 mg (N=26) | Placebo (N=10) | IMR-687 50 mg/100 mg (N=25) | IMR-687 200 mg (N=24) |
| Sickle cell anemia crisis | 14 (70.0) | 6 (50.0) | 14 (53.8) | 7 (70.0) | 10 (40.0) | 3 (12.5) |
| Headache | 4 (20.0) | 2 (16.7) | 8 (30.8) | 4 (40.0) | 12 (48.0) | 5 (20.8) |
| Nausea | 0 | 2 (16.7) | 8 (30.8) | 5 (50.0) | 4 (16.0) | 3 (12.5) |
| Back pain | 2 (10.0) | 0 | 6 (23.1) | 2 (20.0) | 1 (4.0) | 4 (16.7) |
| Upper respiratory tract infection* | 2 (10.0) | 3 (25.0) | 1 (3.8) | 2 (20.0) | 2 (8.0) | 1 (4.2) |
| Abdominal Pain | 1 (5.0) | 1 (8.3) | 6 (23.1) | 0 | 4 (16.0) | 2 (8.3) |

*includes nasopharyngitis

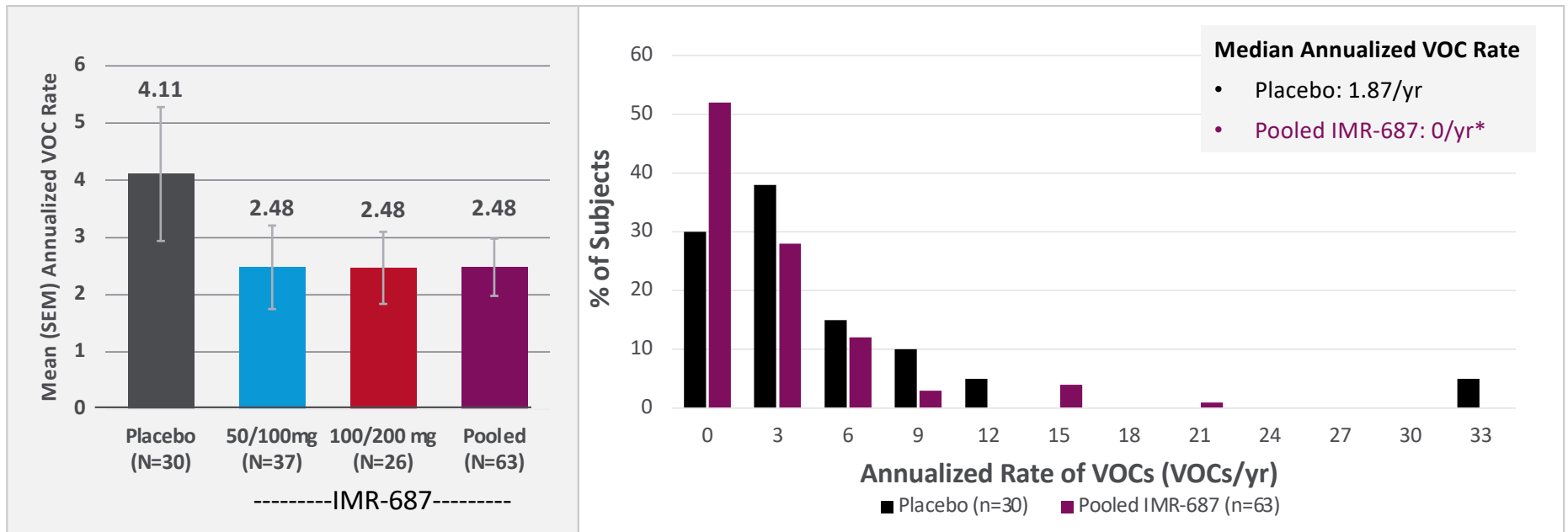
PRELIMINARY DATA

Parent Study (N=93): Annualized VOC Rate Decreased in IMR-687 Groups

- **VOCs**, as captured in safety database, were reduced in IMR-687 groups vs. placebo groups; with/without HU
 - *Mean annualized rate: 40% lower* in pooled treated groups vs. placebo groups
 - *Median annualized rate: 0/yr* in pooled treated groups vs. **1.87/yr** in placebo groups
 - *VOC-related hospitalizations: Mean annualized rate was 0.84/yr* in pooled IMR-687 vs. **1.36/yr** in placebo groups

Mean Annualized VOC Rate

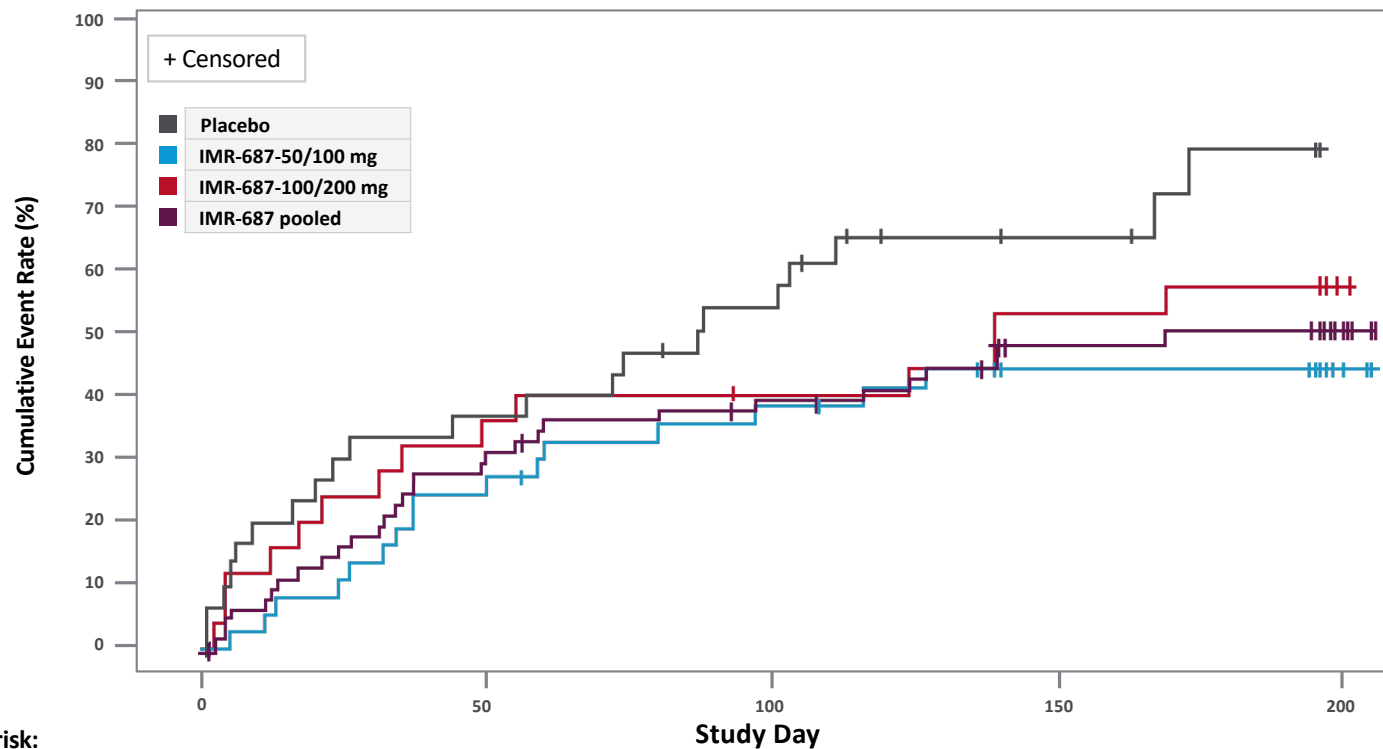
Distribution of Annualized VOC Rate



*p=0.048 by Mood's median test
p=0.077 by Wilcoxon test

Parent Study (N=93): Time to 1st VOC Improved vs. Placebo

- Kaplan-Meier analysis of time to 1st VOC; subjects censored if discontinued prior to having VOC
- Median time to first VOC for pooled IMR-687 groups was significantly longer than placebo groups, **169 days vs. 87 days**, respectively ($p=0.029$)

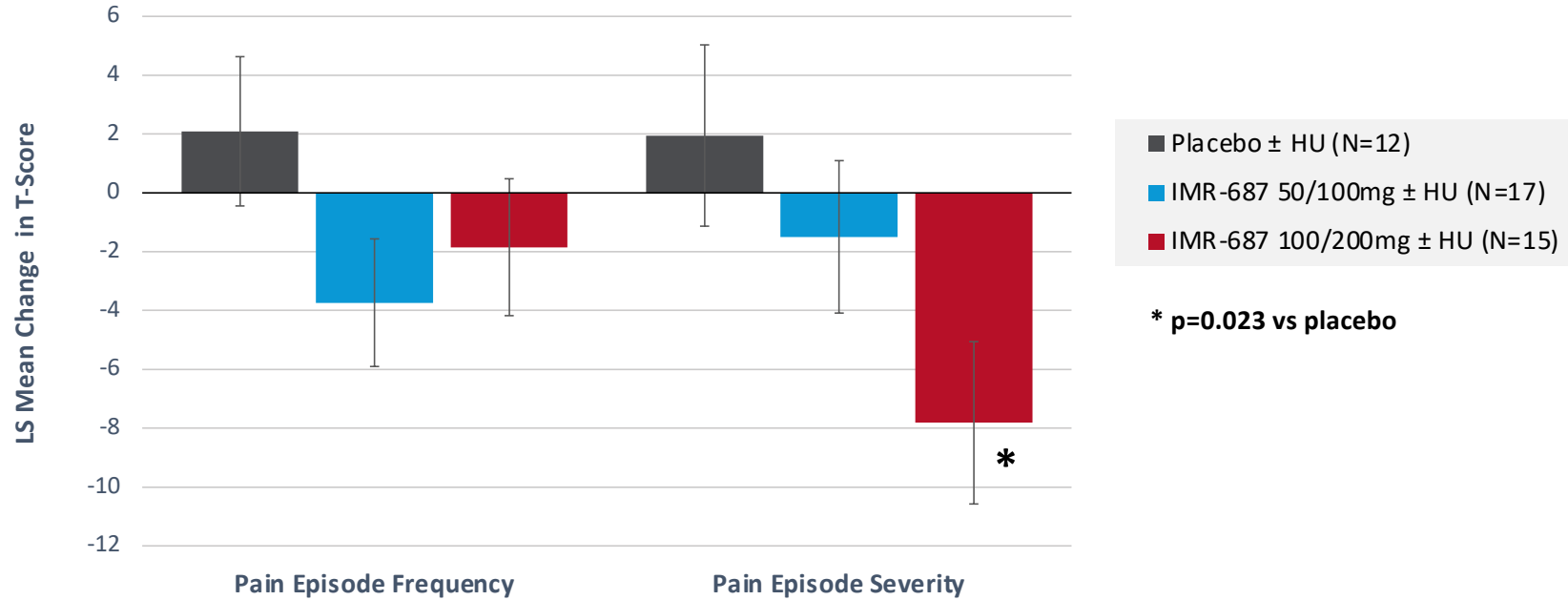


No. at risk:

| | 0 | 50 | 100 | 150 | 200 |
|--------------------|----|----|-----|-----|-----|
| Placebo | 30 | 19 | 13 | 6 | 0 |
| IMR-687-50/100 mg | 37 | 28 | 22 | 12 | 3 |
| IMR-687-100/200 mg | 26 | 16 | 14 | 11 | 2 |
| IMR-687 pooled | 63 | 44 | 36 | 23 | 5 |

Parent Study: ASCQ-Me Pain Episodes Frequency and Severity Improved

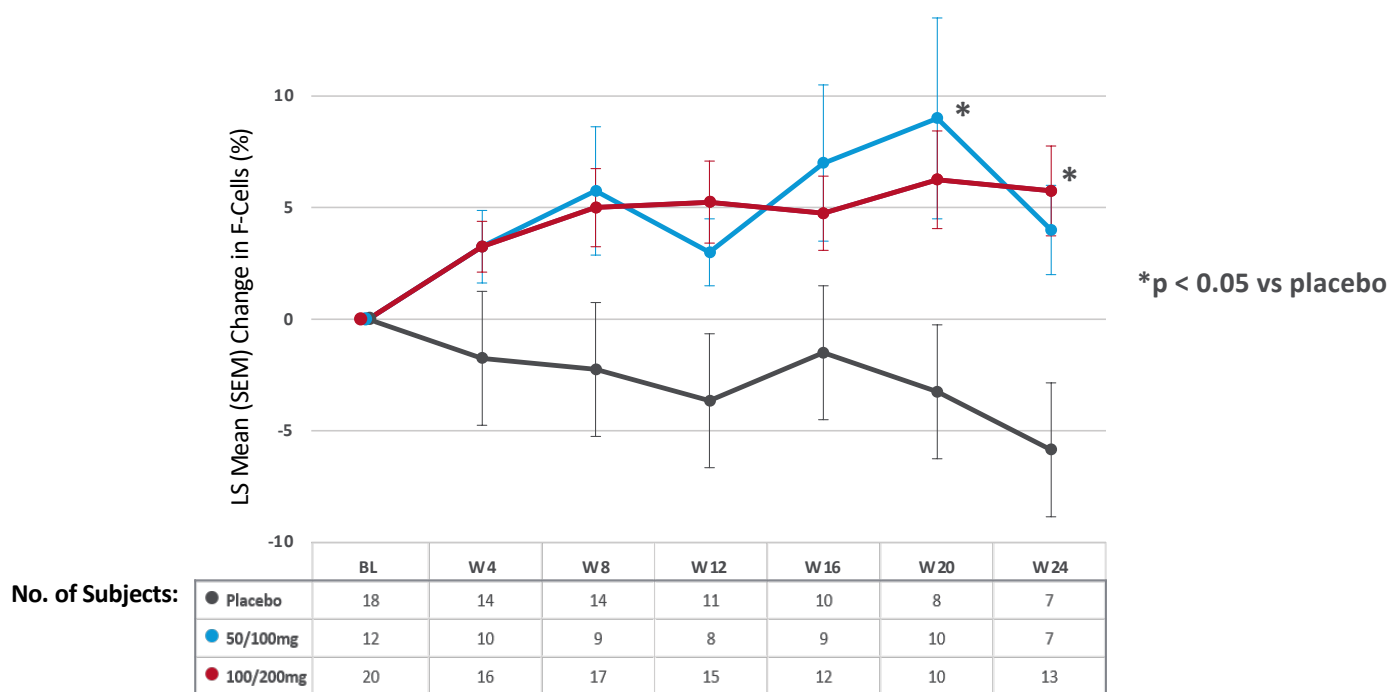
- ASCQ-Me is a validated SCD patient reported outcome (PRO) instrument
 - Two sub-domains report pain episode (VOC) frequency and severity
 - Lower values = improvement



LS Mean (SEM) change from baseline to Week 24 by ANCOVA

Parent Study, IMR-687 Monotherapy: Increase in F-Cells (%) Over Time

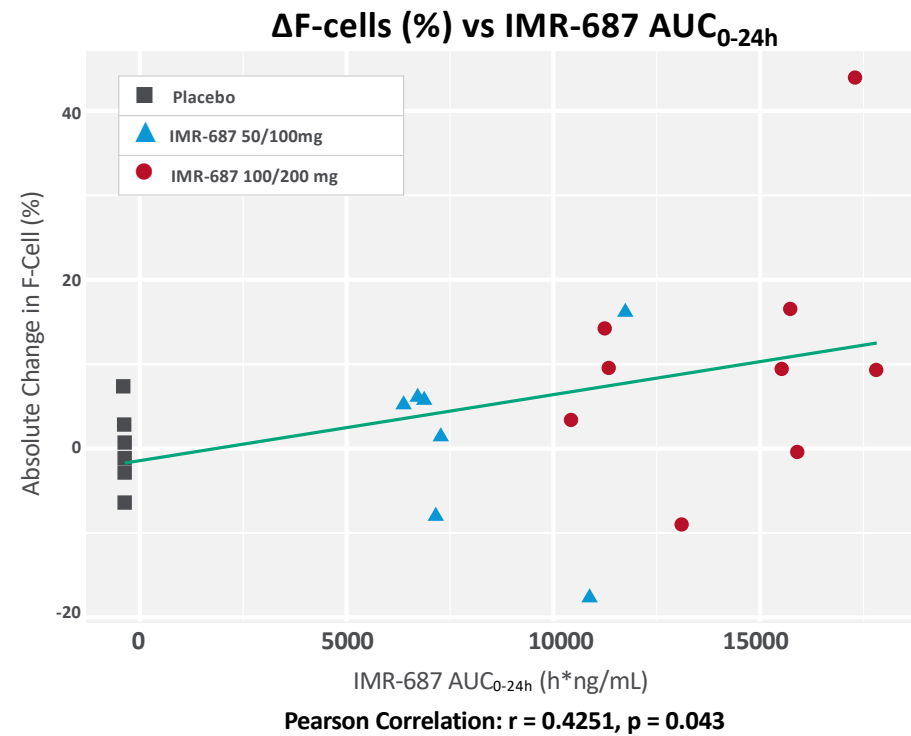
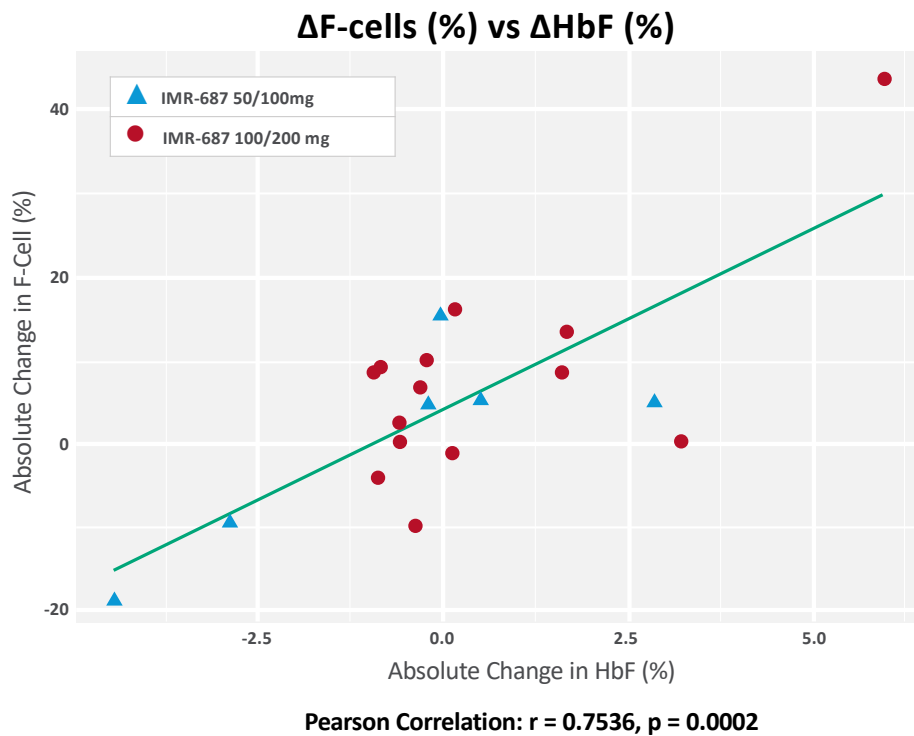
- High dose and low dose groups had increase in % cells containing HbF (F-cells) compared to placebo
- LS mean (SEM) difference between 100/200 mg group and placebo at Week 24 was +11.66 (4.72), $p=0.019$



Absolute LS mean (SEM) change from baseline by mixed model repeated measures (MMRM)

Parent Study, IMR-687 Monotherapy: Correlations of F-cells with HbF, AUC

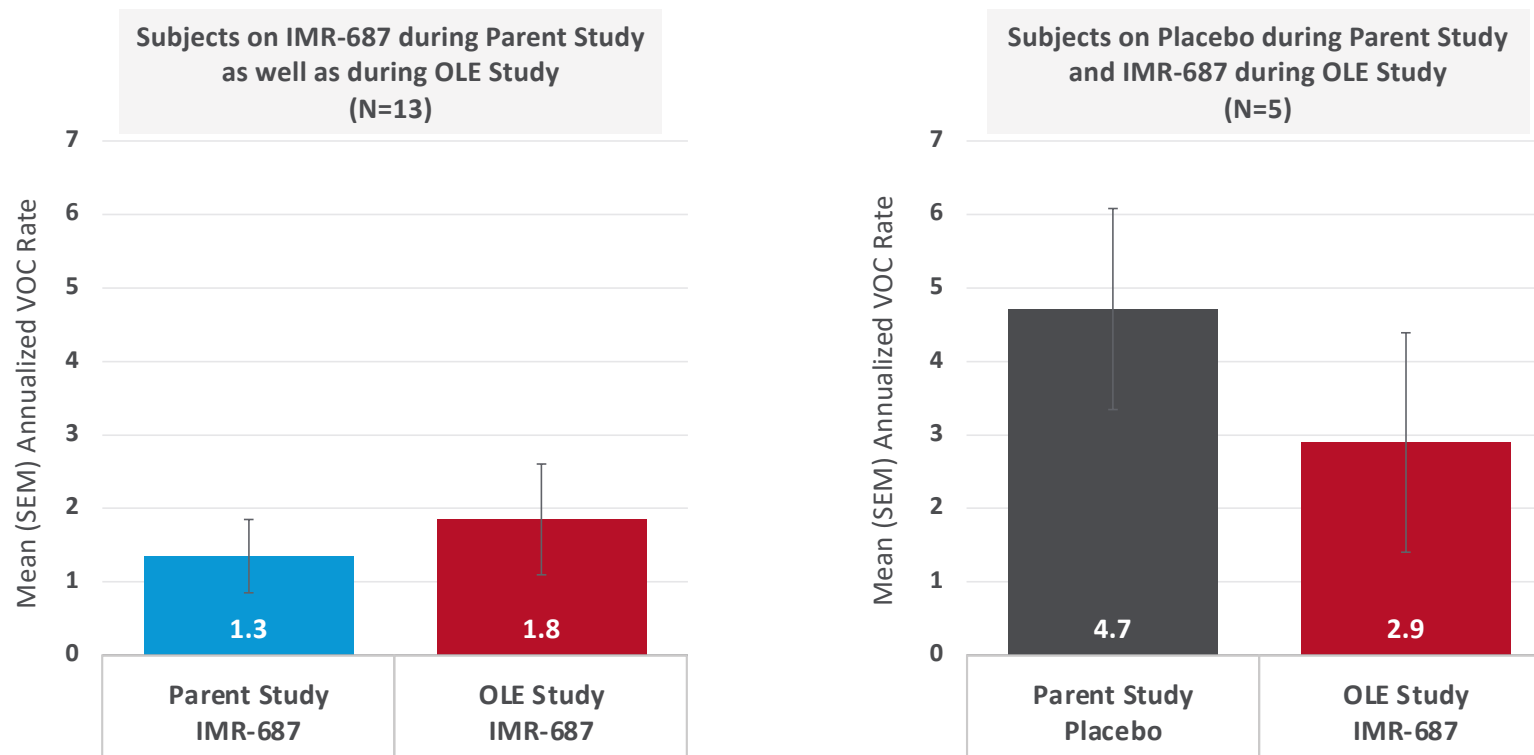
- Absolute change in F-cells (%) from baseline to Week 24 was highly correlated with absolute change in HbF (%), $p=0.0002$
- Absolute change in F-cells (%) from baseline to Week 24 was correlated with IMR-687 exposure (AUC_{0-24h}), $p=0.043$



AUC = Area under curve for IMR-687 concentration

OLE Study: Annualized VOC Rate Compared to Parent Study

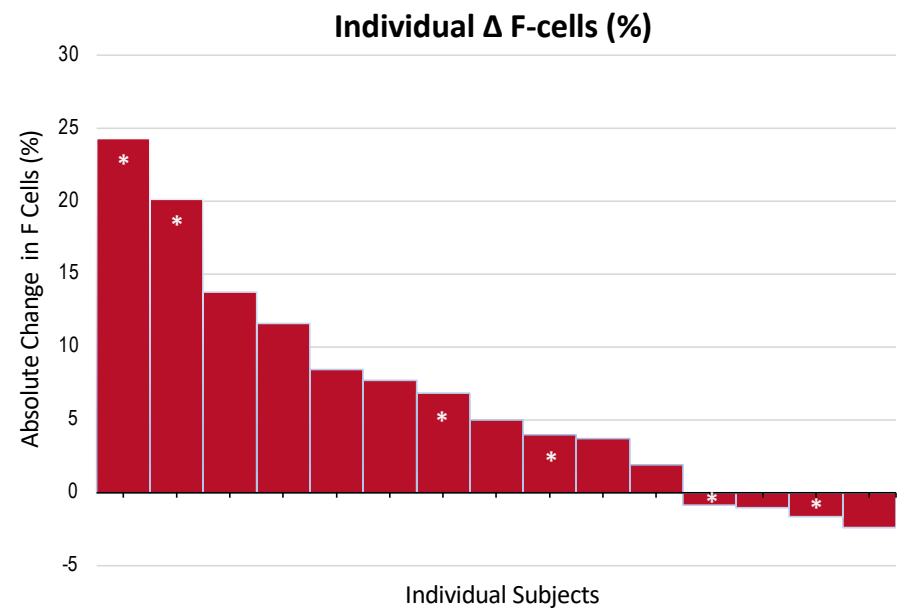
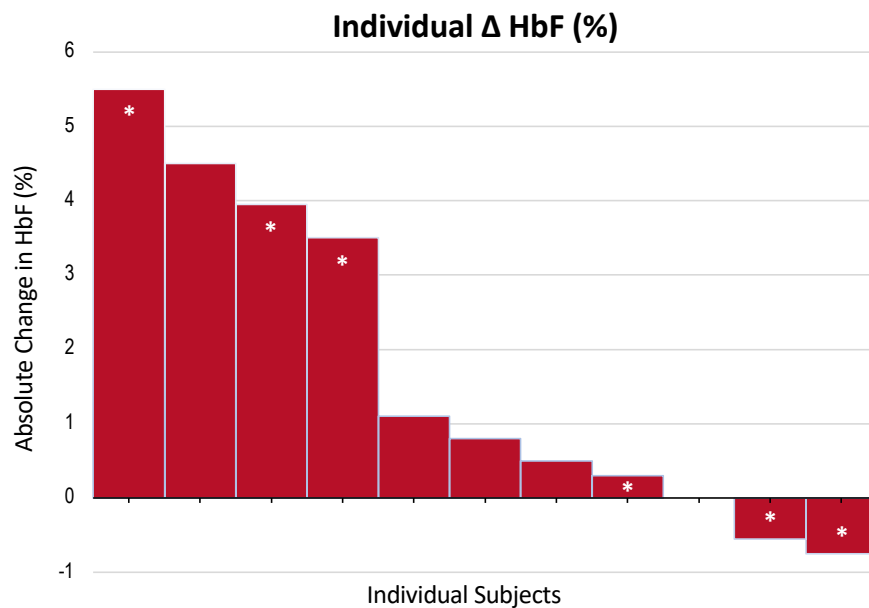
- Includes subjects with or without stable background HU therapy, treated for minimum of 200 days in OLE study (N=18)
- Subjects previously treated with IMR-687 **maintained low VOC rate** in OLE study
- Subjects previously treated with placebo had a **39% reduction** in VOC rate when switched to IMR-687 in OLE study



PRELIMINARY DATA

OLE Study: Absolute Change from Baseline to Mo 8 in HbF (%) & F-cells (%)

- Month 8[#] HbF: **36% of subjects** (4/11) had response $\geq 3\%$ (5.5%, 4.5%, 4.0%, 3.5%)
- Month 8[#] F-cells: **47% of subjects** (7/15) had response $\geq 6\%$
- Minimal change in total Hb; trend for reduction in indirect bilirubin, variable changes in LDH, reticulocytes (data not shown)



* = Subjects without treatment interruption – baseline from parent study used (total treatment 14 months)

= Month 12 values used for one subject with missing Month 8 values

PRELIMINARY DATA

IMR-687 in SCD: Summary & Conclusions

- IMR-687 was well-tolerated as a monotherapy and in combination with HU; most frequent adverse events included headache and nausea
- **Parent study**
 - ~40% lower mean annualized VOC rate in IMR-687-treated groups vs placebo groups; significant difference between median values
 - Significant prolongation in time to first VOC in IMR-687 treated groups vs. placebo groups
 - Reduction in mean annualized hospitalizations for VOCs also observed
 - Improved patient-reported outcomes regarding pain episodes (ASCQ-Me)
 - **PK/PD:** Increases in F-cells (%) correlated with HbF (%) and with IMR-687 exposure
- **Open-label extension (OLE) study**
 - Low VOC rate was maintained in subjects who remained on IMR-687 longer term
 - VOC rate was reduced in subjects previously on placebo in parent study
 - 36% (4/11) subjects increased HbF >3% at Month 8; minimal change in total Hb
- Higher doses up to 400mg of IMR-687 being investigated in ongoing Phase 2b studies

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