(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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DISCLOSURES

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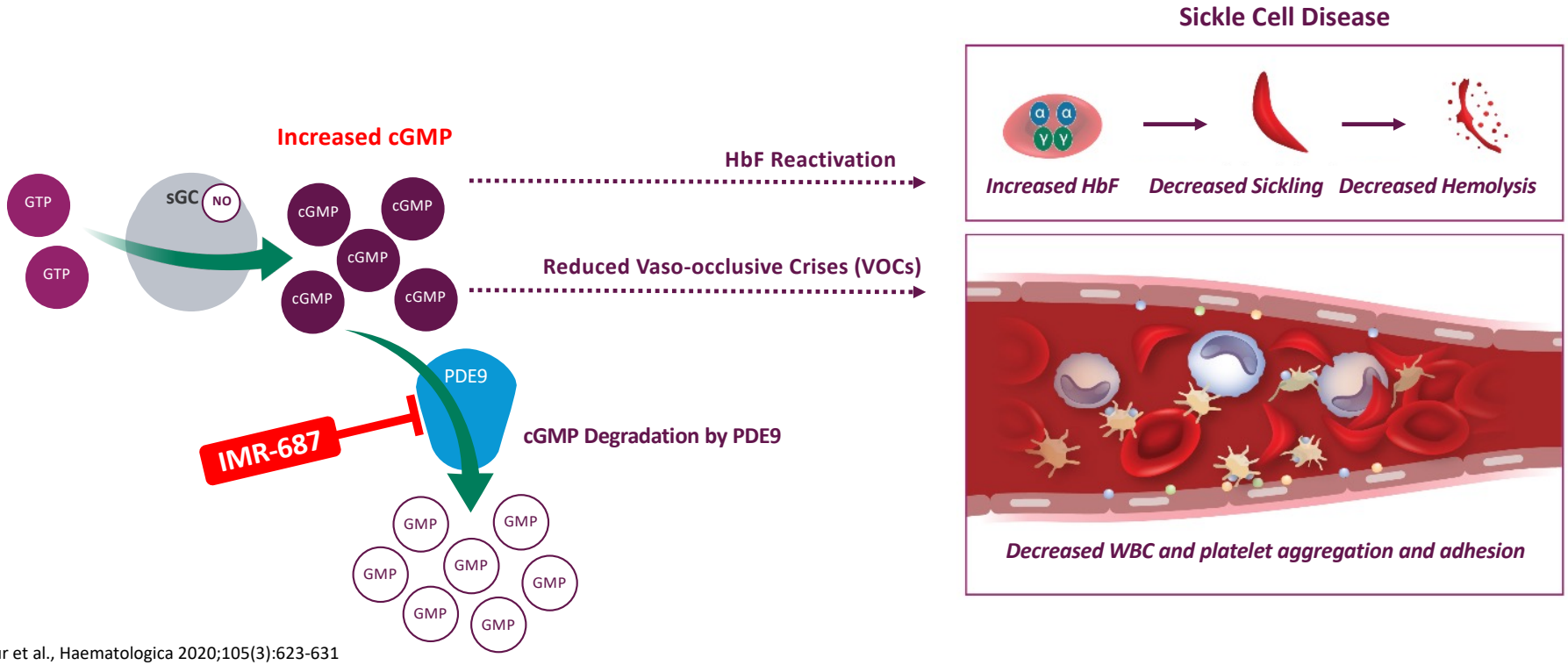
Overview: IMR-687 Multimodal Mechanism of Action in SCD

- 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



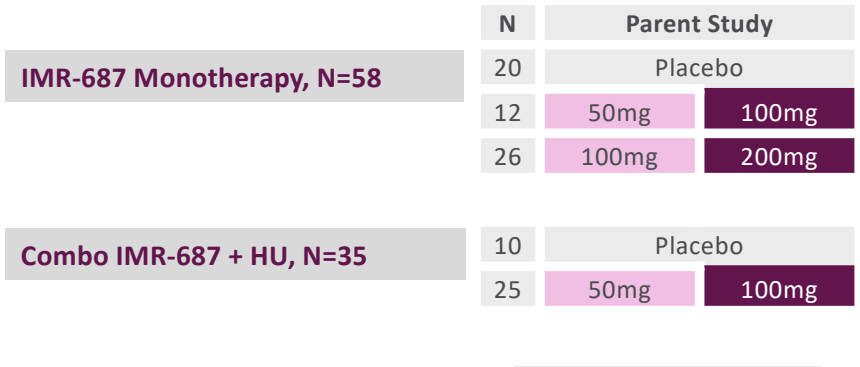
McArthur et al., Haematologica 2020;105(3):623-631

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



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)

*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 ≥ 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 ≥20% subjects in any IMR-687 Group, n (%)

	Parent Study					OLE Study
	IMR-687/Placebo, Monotherapy			IMR-687 + HU/Placebo + HU		IMR-687 ± 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)

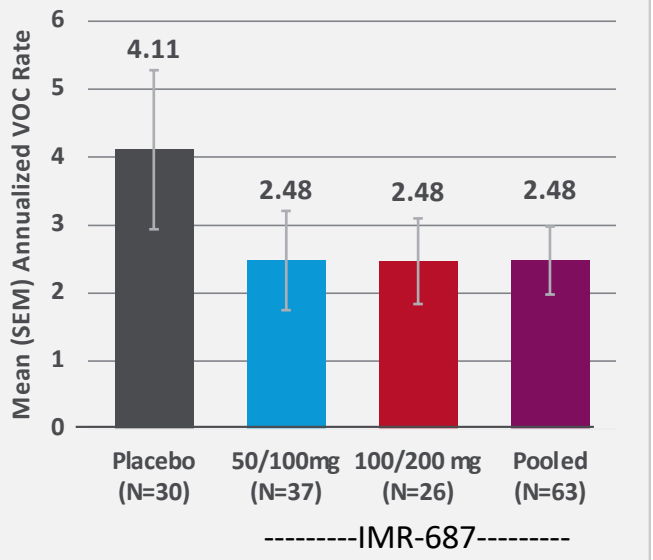
*includes nasopharyngitis

PRELIMINARY DATA

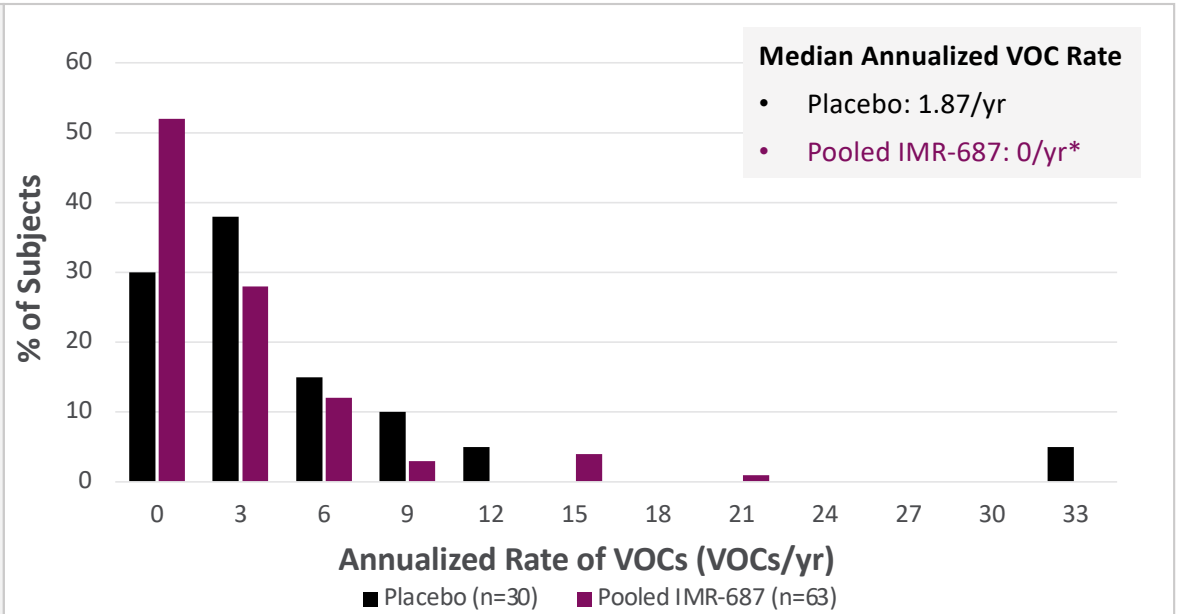
Parent Study (N=93): Annualized VOC Rate Decreased in IMR-687 Groups

- **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



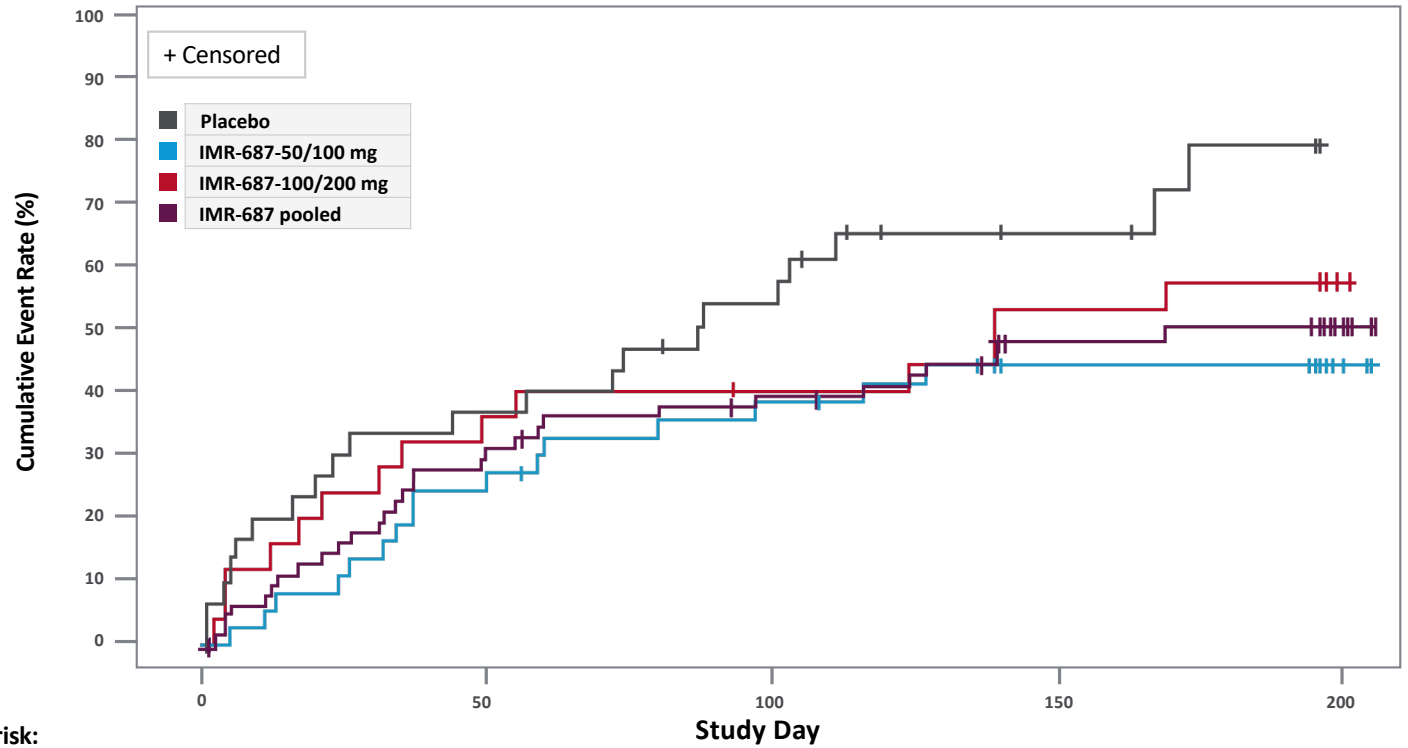
Distribution of Annualized VOC Rate



*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)



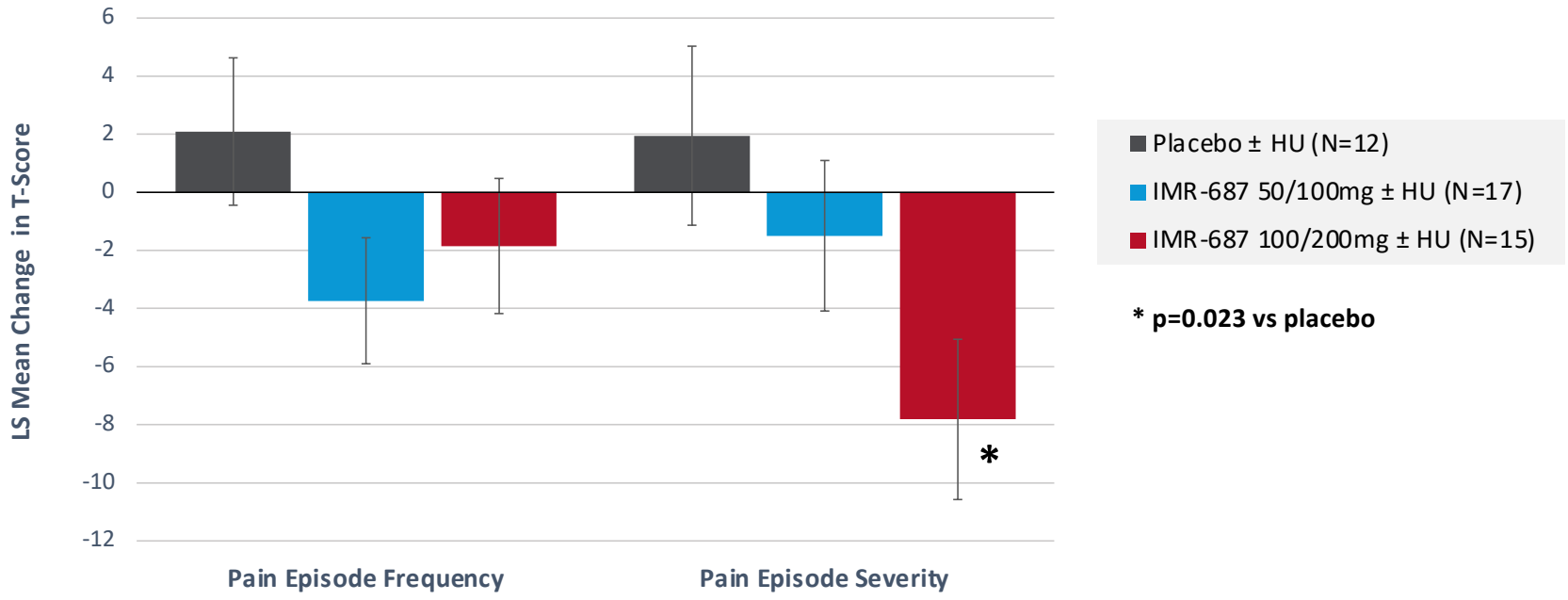
Log-rank p=0.029

No. at risk:

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

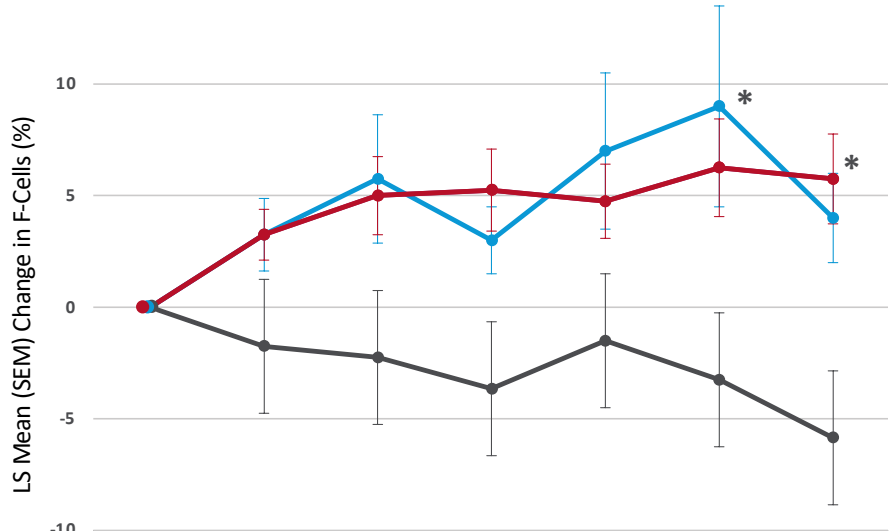
- ASCQ-Me is a validated SCD patient reported outcome (PRO) instrument
  - Two sub-domains report pain episode (VOC) frequency and severity
  - Lower values = improvement



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



*p < 0.05 vs placebo

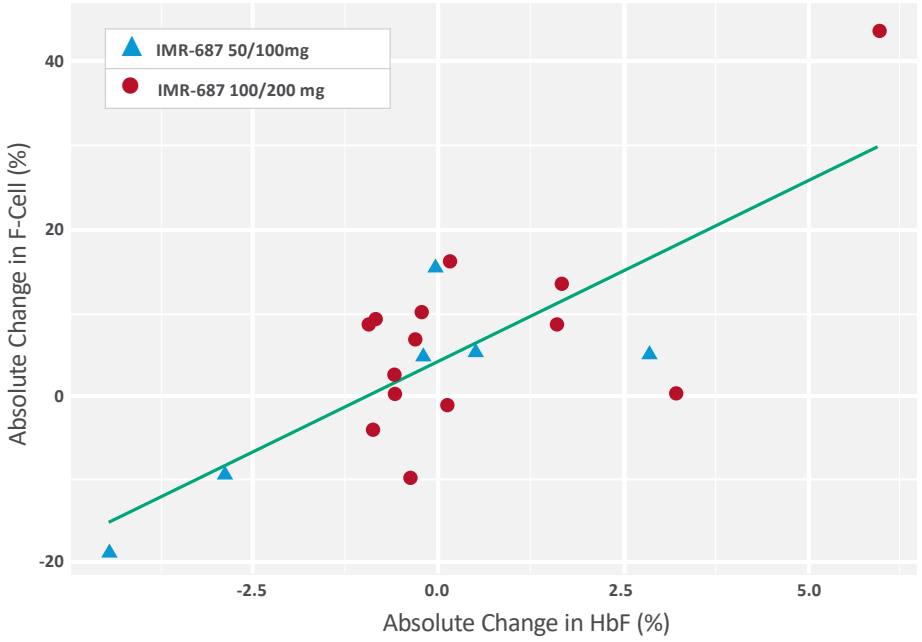
No. of Subjects:	BL	W4	W8	W12	W16	W20	W24
Placebo	18	14	14	11	10	8	7
50/100mg	12	10	9	8	9	10	7
100/200mg	20	16	17	15	12	10	13

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

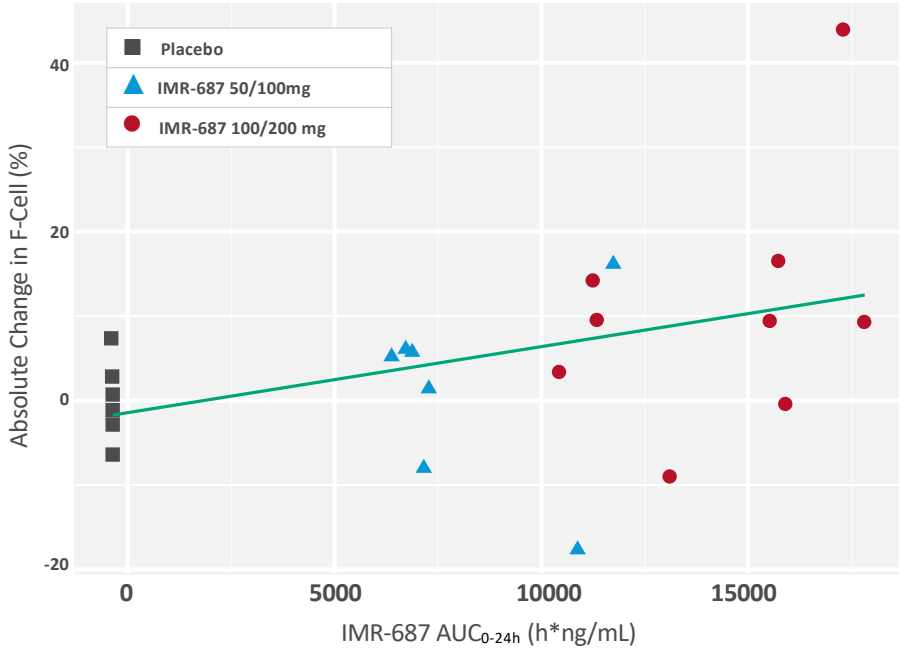
- Absolute change in F-cells (%) from baseline to Week 24 was highly correlated with absolute change in HbF (%), p=0.0002
- Absolute change in F-cells (%) from baseline to Week 24 was correlated with IMR-687 exposure ($AUC_{0\text{-}24h}$), p=0.043

ΔF-cells (%) vs ΔHbF (%)



Pearson Correlation: r = 0.7536, p = 0.0002

ΔF-cells (%) vs IMR-687 $AUC_{0\text{-}24h}$

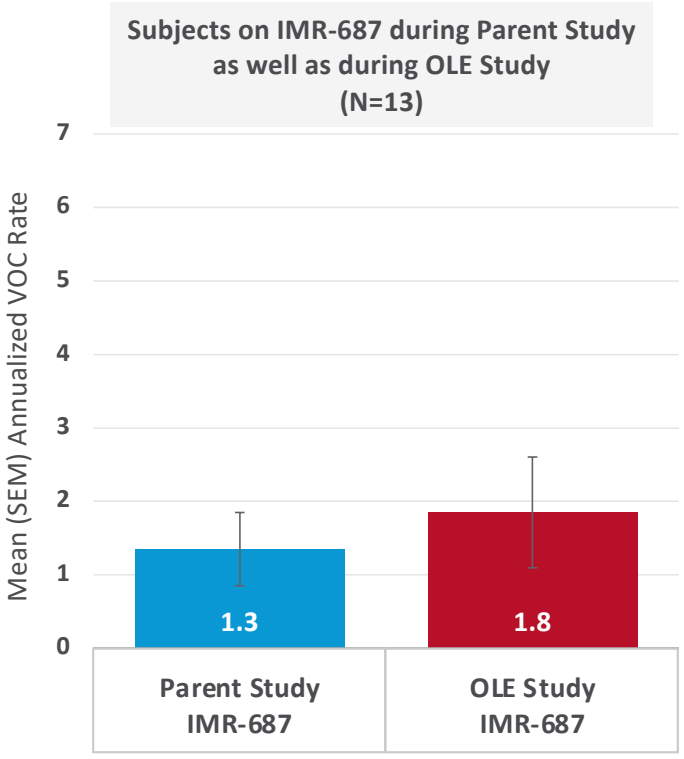


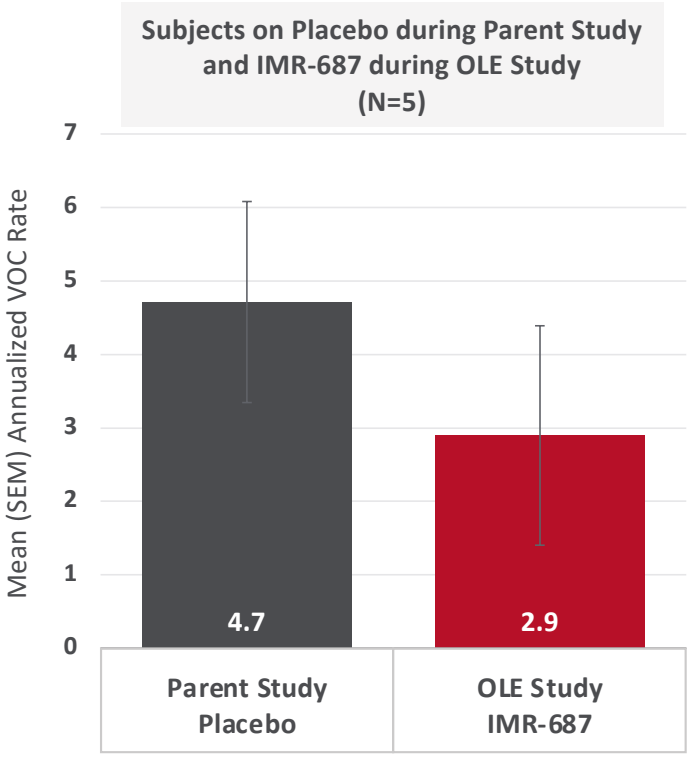
Pearson Correlation: r = 0.4251, p = 0.043

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

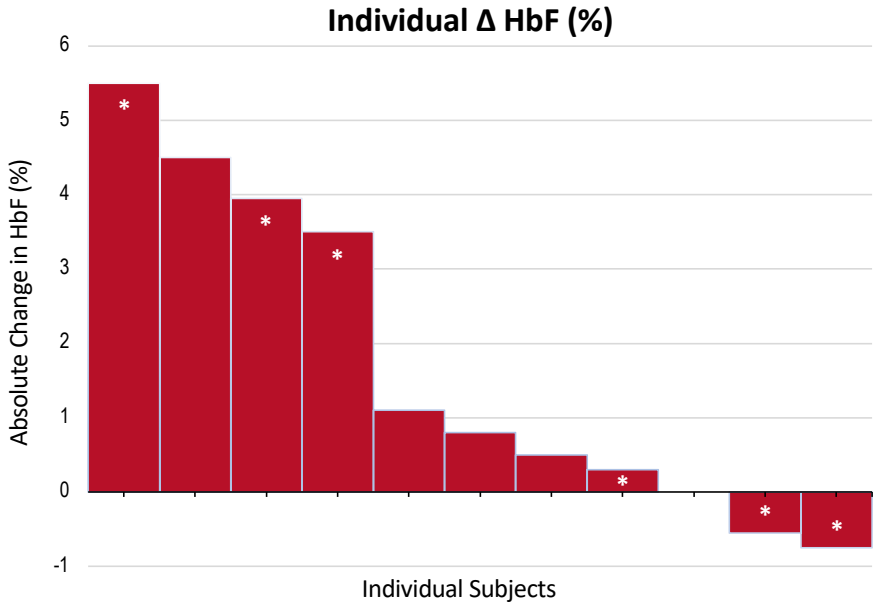


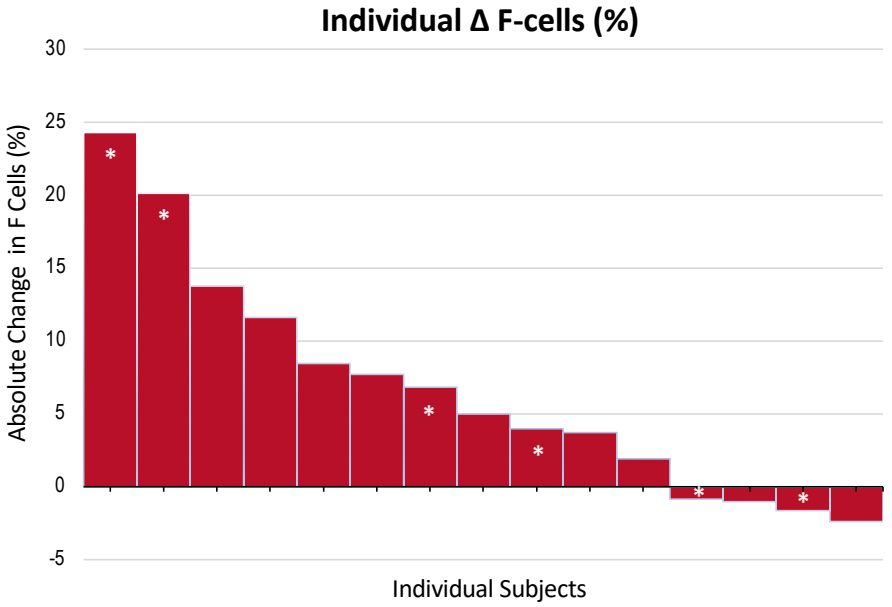


PRELIMINARY DATA

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

- Month 8# HbF: **36% of subjects** (4/11) had response ≥ 3% (5.5%, 4.5%, 4.0%, 3.5%)
- Month 8# F-cells: **47% of subjects** (7/15) had response ≥ 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

PRELIMINARY DATA

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