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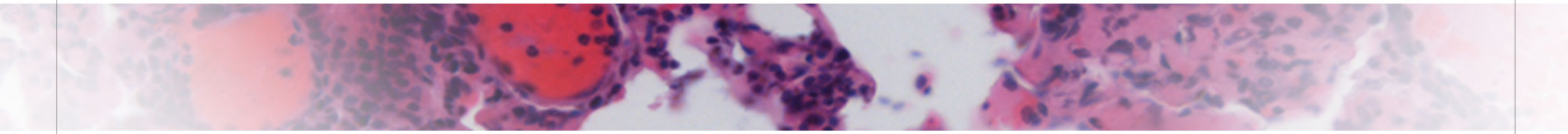

Benefits and Safety of Long-Term Use of IMR-687 As Monotherapy or in Combination with a Stable Dose of Hydroxyurea (HU) in 2 Adult Sickle Cell Patients

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Study Background

- IMR-687 is an inhibitor of phosphodiesterase-9 (PDE9) intended to treat SCD by stimulating the production of fetal hemoglobin (HbF)

- IMR-SCD-102-EXT is an open label extension (OLE) study of an ongoing Ph 2a, randomized, double blind, placebo-controlled study of IMR-687 in patients with SCD (homozygous sickle hemoglobin [HbSS] or sickle-β^0 thalassemia). The OLE study examines the benefit/safety of IMR-687 administered for up to 4 years.

- This is a case series with preliminary data as of 8/2020 on the first two OLE patients, both of which have who had been treated on the OLE for ~ 12 months and ~6 months, respectively. Retrospective review of patient medical records allows for comparison of equal time periods prior to and after the start of IMR-687 treatment; for patient-reported outcomes (PROs) and biomarkers, values were compared for the patient's most recent OLE visit and their baseline visit before the first dose of IMR-687

Patient Summary

Patient 1: Mono

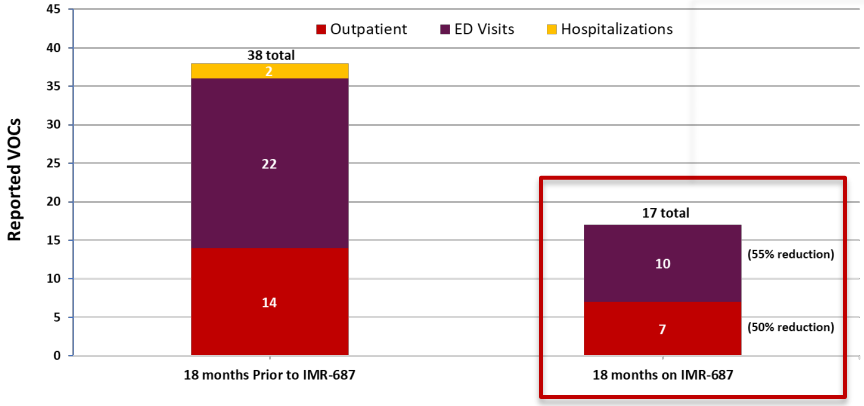
- 28-year-old female diagnosed with HbSS
- **Ph-2a (Mono Arm):** received IMR-687 100 mg once daily for 3 months, then escalated to 200 mg qd for 3 months
- **OLE:** After a 1-month safety follow up period, the patient enrolled in the OLE
  - Received IMR-687 100 mg qd for an additional 12 months; and subsequently escalated to 200 mg qd per protocol amendment.

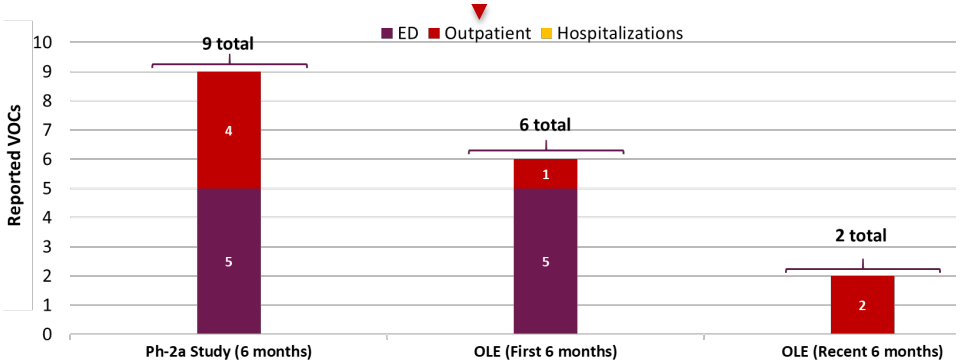
Patient 2: Combo

- 33-year-old female diagnosed with HbSS
- **Ph-2a (Combo Arm):** received placebo for 4 months in the combination Ph 2a sub-study, never received IMR-687
- **OLE:** After a 14-month hiatus, the patient enrolled in the OLE
  - Received IMR-687 for ~6 months: 100 mg qd for 4 months, then escalated to 200 mg qd for ~2 months. The patient was on a stable dose of HU for >18 months prior to OLE study and has remained on that same dose during the OLE.

Results: Patient #1

- 55% reduction in VOCs in 18 months on IMR-687 (17) **vs**. 18 months prior to treatment (38); reduced ED visits and hospitalizations
- VOCs reduce over time: Of 17 VOCs while on IMR-687, 2 were in most recent 6 months with no ED visits





Results: Patient #1

- **Biomarkers:** Improvement across red cell measures (F-cells, HbF, Hb, MCV, %Retics, ARCs, Indirect Bilirubin, LDH)
- **ASCQ-Me @ 12 months:** scores improved across **5 domains**: **1)** Severity: Sleep, Stiffness, Pain; **2)** improved Pain Episode frequency & severity. There was no change in social functioning severity and emotional severity worsened

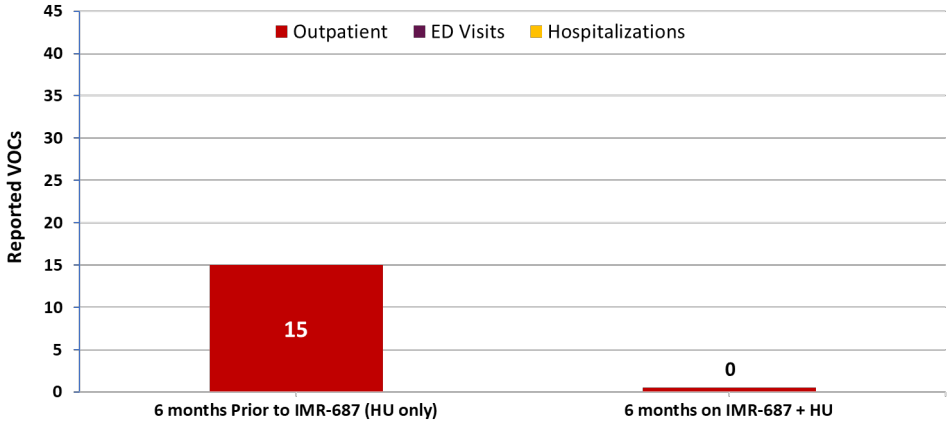
Biomarker	Baseline Ph-2a (October 2018)	Most Recent OLE Visit (June 2020) *[Change from Ph-2a Baseline]*
F-cells (%)	26.1	46.3 [77% increase]
HbF (%)	12.3	16.2 [32% increase]
Hb (g/dL)	7.6	8.6 [13% increase]
MCV (fL)	86.8	90.3 [4% increase]
% Reticulocytes (%)	15	10 [33% decrease]
Absolute Reticulocyte Count (ARCs, x10^9/L)	408	320 [22% decrease]
Indirect Bilirubin (µmol/L)	29	25 [14% decrease]
LDH (U/L)	306	296 [3% decrease]

ASCQ-Me Domain	Baseline Ph-2a (October 2018)	Most Recent OLE Visit (June 2020)
Sleep	High Severity	Low Severity
Stiffness	High Severity	Low Severity
Pain	Middle Severity	Low Severity
Social Functioning	Low Severity	Low Severity
Emotional	Low Severity	High Severity
Pain Episode Frequency*	Poor/Fair	Very Good/Excellent
Pain Episodes Severity*	Good	Very Good/Excellent

*ASCQ-Me Scoring: User's Manual by General Health Ratings (Exhibit 4.3, Page 19)

Results: Patient #2

- 100% reduction in VOCs in 6 months on IMR-687 + HU **vs**. 6 months on same dose of HU
- Improvement in biomarkers: F-cells, HbF, Hb, markers in hemolysis; augmented background HU benefits
- Decrease seen in opioid use (morphine sulfate immediate release) while on IMR-687+ HU vs. HU alone



Biomarker	Baseline OLE Visit (February 2020)	Most Recent OLE Visit (July 2020) *[Change from OLE Baseline]*
F-cells (%)	59.7	80.9 [35.5% increase]
HbF (%)	20.7	29.7 [43.5% increase]
Hb (g/dL)	9.9	10.7 [8.1% increase]
MCV (fL)	111.9	122.1 [9.1% increase]
% Reticulocytes (%)	4.2	3.8 [9.5% decrease]
Absolute Reticulocyte Count (ARCs, x10^9/L)	102.5	89.8 [12.4% decrease]
Indirect Bilirubin (µmol/L)	12	11 [8.3% decrease]
LDH (U/L)	332	245 [26.2% decrease]

Conclusions

- A case series of the first 2 patients enrolled on the IMR-SCD-102 EXT study and treated with IMR-687, showed it has been well-tolerated in both patients.

- Furthermore, after ~12 months (patient #1) and ~6 months (patient #2) on the OLE, administration with IMR-687 showed sustained increases in F-cells/HbF, better clinical outcomes, and improved SCD biomarkers, including Hb and measures of hemolysis.

- These preliminary results potentially show that extended duration of treatment with IMR-687 (6 months and beyond) could be beneficial to SCD patients as a monotherapy or in combination with HU.