EHA25 VIRTUAL
25th Congress of the European Hematology Association VIRTUAL EDITION
IMR-687: A HIGHLY SELECTIVE PHOSPHODIESTERASE 9 INHIBITOR (PDE9i), INCREASES F-CELLS & FETAL HEMOGLOBIN IN A PH-2A INTERIM ANALYSIS

Biree Andemariam*1, Willem Scheele 2, Victor Gordeuk3, Jo Howard 4, Julie Kanter 5, Perla Eleftheriou 6, Shivan Pancham 7, Robert Hagar 8, Lois Clarke 9, Gershwin Blyden 10, Kevin Johnson 2, Eleanor Lisbon 2, Rahul Ballal 2

1University of Connecticut Health, Farmington, CT, USA, 2Imara, Boston, MA, USA, 3University of Illinois, Chicago, IL, USA, 4Guy's and St Thomas', London, UK, 5University of Alabama, Birmingham, AL, USA, 6University College London Hospital, London, UK, 7Sandwell & West Birmingham Hospital, Birmingham, UK, 8UCSF Benioff Children's Hospital, Oakland, CA, USA, 9Loretto Hospital, Chicago, IL, USA, 10Foundation for Sickle Cell Disease, Hollywood, FL, USA

June 12, 2020
New Therapeutic Approaches for Sickle Cell Disease
EHA-1412
Disclosure

**Advisory Board:** bluebird bio, CRISPR/Vertex, Cyclerion, GBT, Hemanext, Pfizer, Novartis, NovoNordisk, Terumo

**Research Funding:** Imara (IMR-687 phase 2A study), Novartis (Spartan study)

Tuesday May 26th, 2020
New Therapeutic Approaches for Sickle Cell Disease
EHA-1412
Forward-Looking Statements

This presentation may contain forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to, (i) statements relating to the design and timing of the Company’s Phase 2b clinical trial evaluating IMR-687 in patients with sickle cell disease, (ii) the timing for reporting data from the ongoing Phase 2a clinical trial evaluating IMR-687 in patients with sickle cell disease and (iii) the therapeutic potential of IMR-687 and advancement of the Company’s clinical program. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: the impact of extraordinary external events, such as the risks and uncertainties resulting from the impact of the COVID-19 pandemic on the Company’s business, operations, strategy, goals and anticipated milestones, including its ongoing and planned research activities and ability to conduct and readout data from its ongoing Phase 2a clinical trial of IMR-687 in sickle cell disease and its ability to initiate, enroll, dose and readout data from its planned Phase 2b clinical trial of IMR-687 in sickle cell disease; the Company’s ability to advance the development of IMR-687 under the timelines it projects in current and future clinical trials, demonstrate in any current and future clinical trials the requisite safety and efficacy of IMR-687, replicate scientific and non-clinical data in clinical trials, obtain and maintain necessary regulatory approvals, obtain, maintain and enforce necessary patent and other intellectual property protection, identify, enter into and maintain collaboration agreements with third parties, manage competition, manage expenses, raise the substantial additional capital needed to achieve its business objectives, attract and retain qualified personnel, and successfully execute on its business strategies; and other factors discussed in the “Risk Factors” section of the Company’s most recent Quarterly Report on Form 10-Q, which is on file with the Securities and Exchange Commission and in other filings that the Company makes with the Securities and Exchange Commission in the future. Any forward-looking statements contained in this presentation speak only as of the date hereof, and the Company expressly disclaims any obligation to update any forward-looking statement, whether as a result of new information, future events or otherwise.
A randomized, double-blind, placebo-controlled study of IMR-687 in adult patients with sickle cell anemia

(Homozygous HbSS or Sickle-β0 Thalassemia)
• IMR-687 is a selective, potent inhibitor of phosphodiesterase-9 (PDE9)
• Inhibiting PDE9 increases cGMP (1)
  – Leads to increases in HbF as well as reductions in RBC sickling, WBC adhesion and occlusion of blood vessels
• PDE9 is in a similar pathway as Hydroxyurea (HU)
  – PDE9 has a direct effect on cGMP production, which may confer a more efficient/effective therapeutic response
  – Does not induce myelosuppression like HU
  – Pathway may be synergistic with HU (2)

(1) Cyclic guanosine monophosphate (“cGMP”)
Ph-2a Objectives

**Primary Objective**

- Assess the safety and tolerability of IMR-687 in adult patients with sickle cell anaemia (SCA) who are not receiving hydroxyurea (HU) and in those adults receiving a stable dose of HU.

**Exploratory**

- To assess the potential efficacy of IMR-687 on SCA-related clinical outcome measures in both monotherapy and combo HU populations. Some of these measures include:
  - Hemoglobin F (%) and F cells (%)
  - Total hemoglobin (Hb) levels
  - Adhesion molecules (P-selectin, sE-selectin, sVCAM)
  - Clinical outcomes: pain-related measures, sickle cell related events requiring health care, transfusions, etc.
  - Patient Reported Outcome Questionnaire (ASCQ-Me)
Ph-2a Inclusion/Exclusion Criteria

**INCLUSION**
- 18-50 years old
- Confirmed HbSS or Sickle-\(\beta^0\)-Thalassemia
- WOCBP must be abstinent or on highly effective contraception
  - In Population A: Have not received HU within 90 days prior to screening and are not planning to take HU within the next 6 months.
  - In Population B: Have received HU for at least 6 months, and on a stable dose for at least 60 days prior to screening.

**EXCLUSION**
- Haemoglobin <6 or >12 g/dL
- >7 hospital admissions (>24 hrs) for vaso-occlusive crises (VOC), including acute chest syndrome (ACS) and priapism, within the last year.
- Reticulocytes <100 for Pop A, <80 for Pop B
- Transfusion within 60 days of first dose
- eGFR <50 ml/min/m²
- AST/ALT >3x upper limit of normal
- Total body weight < 50kg
Ph-2a: Double-Blind, Randomized, Placebo-Controlled Trial

- **Monotherapy (Pop A):**
  - 3-arm titrated study (1:1:1 Randomization)
  - 6-month duration
  - SRC review & dose escalation at 3 months

- **Combo Therapy + HU (Pop B):**
  - 2-arm study (2:1 Randomization)
  - 4-month duration
  - SRC review & dose escalation at 1 month

- **Protocol Driven Interim Analysis:** when 18 monotherapy patients completed 6 months; all data across study analyzed
IMR-687 was well tolerated; expected increases in GI disorders in active arms vs. placebo

- Minimal differences across most organ systems, few differences in placebo vs. IMR-687 active arms
- **Blood and Lymphatic Disorders**: No neutropenia observed in 50/100mg or 100/200mg arms (0%)
- **Vitals**: no observed changes in heart-rate, blood pressure, respiratory rate
- **GI Disorders** were increased 50/100mg (27.3%) arm & 100/200mg arm (58.3%) vs. placebo arm (14.3%)
  - **Time course of AEs in 100/200mg**: 10 of 11 eleven events occurred @100mg dose vs. 1 event @200mg
  - **Grade of AEs in 100/200mg**: 8/11 events were mild (72%); remaining 3 events were moderate (same patient)
- Fewer % of patients reported VOCs: 50% in placebo, 45.5% in 50/100mg, 41.7% in 100/200mg
  - Ph-2a was not a powered VOC study; early clinical data (to be further explored in next study)
Ph-2a Combo (n=20): Safety Summary

IMR-687 was well tolerated when dosed in combination with HU and IMR-687

- Minimal differences across most organ system classes, few observable differences in HU vs. HU+IMR-687 arms

- **Blood and Lymphatic Disorders**: No neutropenia observed in combination of IMR-687 + HU (0%)

- **Vitals**: no observed changes in heart-rate, blood pressure, respiratory rate

- **GI Disorders in combo HU+IMR-687 arm were lower than HU arm**: 50/100mg (30.8%) vs. HU only arm (42.9%)

- **Fewer % of patients reported VOCs in combo arm than HU arm**: 50/100mg (38.5%) vs. HU only arm (71.4%)
  - Ph-2a was not a powered VOC study; early clinical data (to be further explored in next study)
Rationale: Shared pathway with IMR-687 and HU prompted PK analysis to ensure IMR-687 did not impact HU PK

Design
- **Step 1:** Pre-dose HU PK taken prior randomization (Lead-in 1, 2)
- **Step 2:** PK in combo IMR-687 + HU taken at 2 time points: Day 29, Day 113

Results: No reduction in HU PK observed when combined with IMR-687 treatment
Treatment with monotherapy IMR-687 associated with statistically significant increases in F-cells

- Interim analysis of 37 patients treated (monotherapy); statistical significance achieved for 100/200mg dose ($p=0.022$)

- **100/200mg arm:** patients started at baseline of 13.6% and ended at 31.7% F-cells (relative change of 18.1%)

- **Dose Dependent:** F-cells increased post-dose escalation, continued increases seen in 100/200mg arm (week 13-25 in graph)
Ph-2a Mono: %HbF Increases with IMR-687

Treatment with monotherapy IMR-687 associated with increased in %HbF

- Interim analysis of 37 patients treated (monotherapy); HbF increased by 1.7% in 100/200mg dose group

- **100/200mg arm**: patients started at baseline of 6.7% and ended at 8.4% HbF (relative change of 1.7%)

- **Dose Dependent**: HbF increased post-dose escalation, continued increases seen in 100/200mg arm (week 13-25 in graph)
Conclusions & Next SCD Study

- **Safety:** IMR-687 was well tolerated as a monotherapy and in combination with HU; no neutropenia seen in mono or combo arms; encouraging trends in reducing VOCs

- **Efficacy:** statistically significant increase in F-cells (p=0.022); increases in mean HbF of 1.7% at the higher dose, data show dose dependent increases @ 200mg

- **Next Steps:** Ph-2a data expected in Q4-2020; new Ph-2b SCD study initiated (52 sites)
  - Higher dose (up to 400mg) and longer duration (1-year); pre-defined VOC definition with FDA
  - Statistically powered @ primary endpoint to see 3% HbF increase in active arms vs. placebo
  - Stratified for region and HU use, mono and combo are same dose/duration (sub-study removed)
  - No dose titration; patients stay on fixed dose of IMR-687 for the duration of study
  - Ph-2b interim data in first half of 2021