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Trials in Progress: The THRIVE Studies Evaluating the Efficacy, Safety, and Long-Term Treatment With Inclacumab, a P-Selectin Inhibitor, in Patients With Sickle Cell Disease

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BACKGROUND

- Sickle cell disease (SCD) is characterized by polymerization of sickle hemoglobin, which triggers red blood cell damage and sickling, leading to chronic hemolysis, anemia, and vasculopathy.[1,2]
- In SCD, recurrent episodes of vaso-occlusive crises (VOCs) caused by the adhesion of leukocytes and sickled red blood cells to the vascular endothelium result in pain, vascular obstruction, tissue ischemia, and inflammation that ultimately contribute to chronic organ damage.[1,3]
- P-selectin is a cell adhesion molecule expressed on the surface of activated platelets and endothelial cells; it is implicated in the pathogenesis of vaso-occlusion.[4-6]
- Inclacumab, an investigational fully human monoclonal antibody, previously developed for cardiovascular disease, targets P-selectin–mediated vaso-occlusion and thus has the potential to reduce the rate of VOCs.[7-9]
- The safety, pharmacokinetics (PK), and pharmacodynamics of inclacumab, manufactured by Global Blood Therapeutics, were evaluated in a phase 1 study in which a single dose of 20 mg/kg or 40 mg/kg intravenous (IV) inclacumab was administered to healthy participants.[10]
  - Inclacumab showed a well-tolerated safety profile for up to 29 weeks post-dose.
  - Plasma inclacumab exposures were dose proportional over the dose range studied, with apparent nonlinearity below approximately 10 µg/mL, suggestive of target-mediated drug disposition (**Figure 1**).
  - Sustained inhibition of ex vivo thrombin receptor–activating peptide (TRAP)-activated platelet leukocyte aggregate (PLA) formation was observed for up to 23 weeks post-dose at both dose levels (**Figure 2**).
  - These results support a phase 3 dose of 30 mg/kg every 12 weeks in patients with SCD experiencing VOCs.

OBJECTIVE

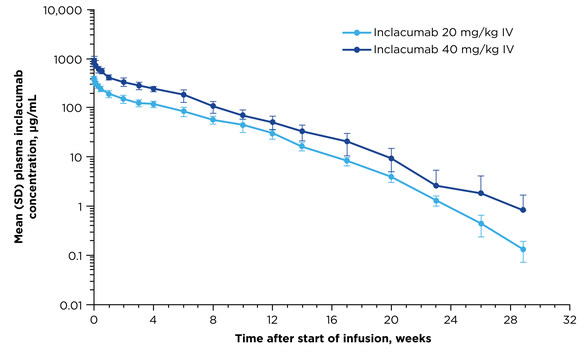
- The Therapeutic Potential of Inclacumab for the Reduction of VOC Episodes (THRIVE) studies include 2 global, multicenter, phase 3 studies and an open-label extension (OLE) study that aim to evaluate the efficacy, safety, and pharmacology of inclacumab in individuals with SCD.

Presented at the
European Hematology Association 2022 Hybrid Congress;
June 9-12, 2022; Vienna, Austria, and virtual.

METHODS

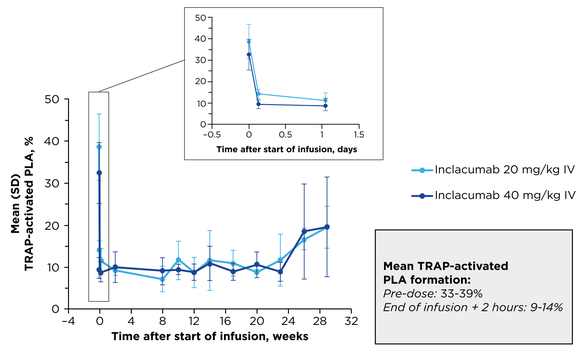
- The THRIVE-131 (NCT04935879) and THRIVE-132 (NCT04927247) phase 3 randomized, double-blind, placebo-controlled trials (**Table 1**) will be conducted at approximately 75 study sites globally (**Figure 3**).
  - In both studies, eligible participants are ≥12 years old, diagnosed with SCD (HbSS, HbSC, HbSβ^0, and HbSβ$^+$ genotypes in THRIVE-131 and all SCD genotypes in THRIVE-132), and have experienced 2 to 10 VOCs in the previous year.
  - Participants in THRIVE-131 will be randomized 1:1 to receive IV inclacumab or placebo every 12 weeks (4 treatments total); the primary endpoint is the rate of VOCs during the treatment period (**Figure 4**).
  - Participants in THRIVE-132 will be randomized 1:1 to receive a single dose of IV inclacumab or placebo within 5 days of resolution of an index VOC that required admission to a healthcare facility and administration of parenteral pain medication; the primary endpoint is readmission for VOC within 90 days of randomization (**Figure 5**).
  - Other outcome measurements for both studies include clinical pharmacology assessments (plasma PK, PLA formation, surface plasmon resonance P-selectin inhibition, and soluble P-selectin).
- THRIVE-133 (NCT05348915) OLE is an OLE study into which participants who have completed either THRIVE-131 or THRIVE-132 have the option of enrolling.
  - The study will evaluate the long-term safety of inclacumab as a therapy for patients with SCD; participants will receive IV inclacumab every 12 weeks as long as the benefit outweighs the risk or until access to inclacumab from an alternative source is available (**Figure 6**).

Figure 1. Plasma Inclacumab Concentration vs Time Profiles Following a Single Dose of IV Inclacumab in Healthy Participants[10]



Quantification of free plasma inclacumab was performed using a validated electrochemiluminescence assay with a lower limit of quantification of 0.01 µg/mL.
IV, intravenous; SD, standard deviation.

Figure 2. TRAP-Activated PLA Formation vs Time Profiles Following a Single Dose of IV Inclacumab in Healthy Participants[10]



Under normal physiological conditions, few platelets are activated and express P-selectin; therefore, the percentage of PLAs is relatively small. PLA modulation by inclacumab is better quantified in ex vivo assays following TRAP upregulation of P-selectin on platelets.
IV, intravenous; PLA, platelet-leukocyte aggregate; SD, standard deviation; TRAP, thrombin receptor–activating peptide.

Figure 3. Site Locations for Phase 3 THRIVE Studies

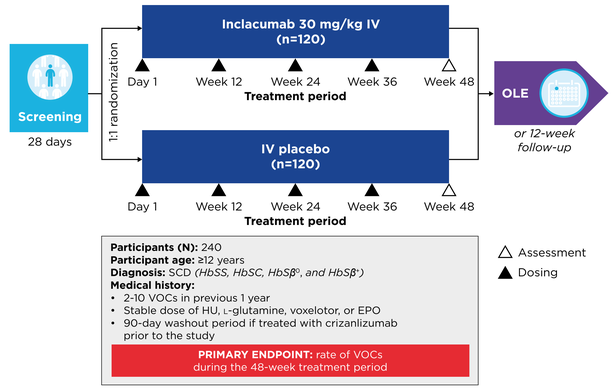
EU, European Union; LATAM, Latin America; MENA, Middle East/North Africa; SSA, Sub-Saharan Africa; USA, United States of America.

Table 1. Comparison of THRIVE-131 and THRIVE-132 Studies

	THRIVE-131	THRIVE-132
Phase	3	3
Study design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
SCD genotype	HbSS, HbSC, HbSβ^0, and HbSβ$^+$	All
Patient age	≥12 years	≥12 years
Randomization and treatment	1:1 Inclacumab 30 mg/kg IV or placebo every 12 weeks for 4 doses	1:1 Single dose of inclacumab 30 mg/kg IV or placebo within 5 days of resolution of index VOC
Primary endpoint	Rate of VOCs during the 48-week treatment period	Readmission for a VOC within 90 days of randomization

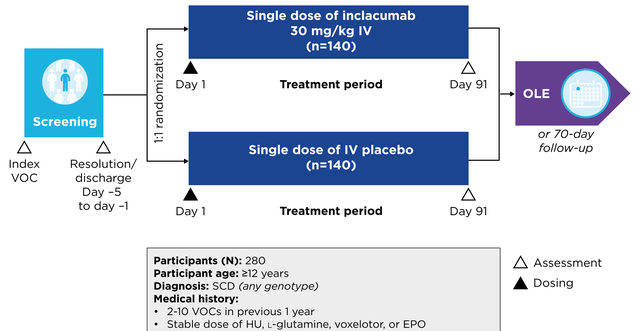
HbSβ^0, sickle beta zero thalassemia; HbSβ$^+$, sickle beta plus thalassemia; HbSC, hemoglobin SC disease; HbSS, homozygous for SCD; IV, intravenous; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Figure 4. THRIVE-131 Study Design



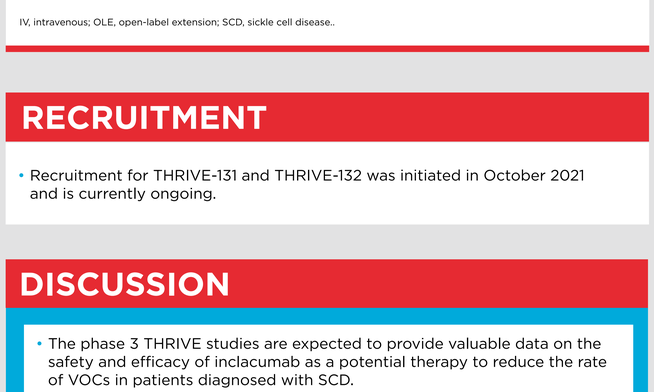
EPO, erythropoietin; HbSβ^0, sickle beta zero thalassemia; HbSβ$^+$, sickle beta plus thalassemia; HbSC, hemoglobin SC disease; HbSS, homozygous for SCD; HU, hydroxyurea; IV, intravenous; OLE, open-label extension; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Figure 5. THRIVE-132 Study Design



EPO, erythropoietin; HbSβ^0, sickle beta zero thalassemia; HbSβ$^+$, sickle beta plus thalassemia; HbSC, hemoglobin SC disease; HbSS, homozygous for SCD; HU, hydroxyurea; IV, intravenous; OLE, open-label extension; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Figure 6. Study Schematic for THRIVE-133 OLE



IV, intravenous; OLE, open-label extension; SCD, sickle cell disease..

RECRUITMENT

- Recruitment for THRIVE-131 and THRIVE-132 was initiated in October 2021 and is currently ongoing.

DISCUSSION

- The phase 3 THRIVE studies are expected to provide valuable data on the safety and efficacy of inclacumab as a potential therapy to reduce the rate of VOCs in patients diagnosed with SCD.
- For questions, please contact THRIVEstudy@gbt.com.

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ACKNOWLEDGMENTS

- **We thank all the patients with sickle cell disease, families, caregivers, and investigators contributing to these studies.**

DISCLOSURES

- **Biree Andemariam:** Consultant, advisory board: Agios, Aruvant, Bluebird Bio, CRISPR, Emmaus, Forma Therapeutics, Global Blood Therapeutics, Hemanext, Novartis, Novo Nordisk, Sanofi Genzyme, Shenox, Terumo BCT, Vertex; research funding: Forma Therapeutics, Global Blood Therapeutics, Hemanext, Imara, Novartis. **Adlette Inati:** Consultant, advisory board: Novartis, Pfizer, Roche, Novo Nordisk, Global Blood Therapeutics, Forma Therapeutics; research funding: Forma Therapeutics, Agios Pharmaceuticals, Global Blood Therapeutics, Imara, AstraZeneca, Novartis, Vifor Pharma, Octapharma. **Raffaella Colombatti:** Advisory board: Bluebird Bio, Novo Nordisk, Global Blood Therapeutics, Novartis, Forma Therapeutics, Addmedica; research funding: Global Blood Therapeutics, Bluebird Bio. **Caterina Minniti:** Consultant: Global Blood Therapeutics, Novartis, Novo Nordisk, Roche, Forma, Agios, Chiesi, Emmaus Life Sciences, Sanguine Bio. **Clark Brown:** Consultant: Global Blood Therapeutics, Imara, Novo Nordisk; research support: Forma Therapeutics, Global Blood Therapeutics, Imara, Novartis. **Kathleen Koeck:** Consultant: Global Blood Therapeutics. **Christina Lourdes Mayer:** Employee: Semivida, Consultant: Global Blood Therapeutics.
- **Mark Davis, Sarah Gray, Carolyn Hoppe, Margot Hottmann, Patrick Yue:** Employees, equity ownership: Global Blood Therapeutics.
- Medical writing and editorial assistance were provided by Brittany Ulrich, PhD (Healthcare Consultancy Group, funded by Global Blood Therapeutics).
- These studies are supported by Global Blood Therapeutics.