RAIN Rare Anaemias International Network

THALASSAEMIA INTERNATIONAL FEDERATION

Rare Anaemias International Network

Clinical Trials Update

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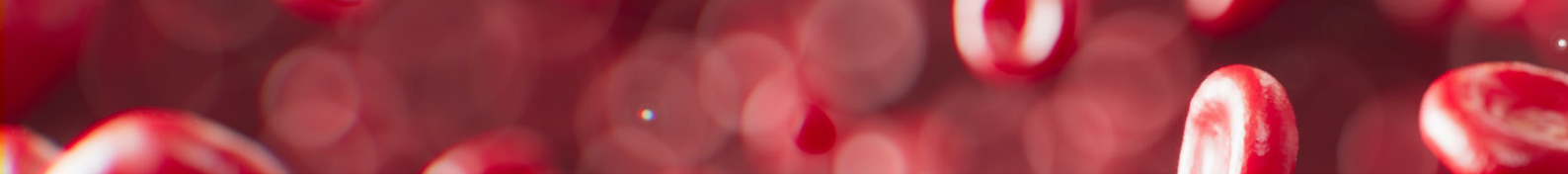


Clinical Trials Update

February 2023

Contents

Ongoing clinical trials for rare anaemias[1]

Table 1. Selection of current clinical trials in rare anaemias

Approach / Target	Disease Area	Trial Phase	Trial Name ; substance	Notable Facts
Improving red cell function	Myelodysplasia (low risk)	N/A	etavopivat	Upcoming
Improving red cell function	Sickle cell disease	Phase 2/3	ENERGIZE ; mitapivat	
Improving red cell function	Sickle cell disease	Phase 2/3	HIBISCUS ; etavopivat	
Improving red cell function	Thalassaemia (transfusion – dependent)	Phase 3	ENERGIZE-T ; mitapivat	
Improving red cell function	Thalassaemia (non-transfusion dependent)	Phase 3	ENERGIZE ; mitapivat	
Improving red cell function	Thalassaemia	Phase 2	etavopivat	
Iron metabolism (hepcidin)	Polycythemia Vera (phlebotomy dependent)	Phase 2	Sapablursen (TMPRSS6)	
Iron metabolism (hepcidin)	Polycythemia Vera	Phase 2	Rusfertide (PTG-300)	
Iron metabolism (hepcidin)	Thalassaemia (non-transfusion dependent)	Phase 2	Apotransferrin	
Iron metabolism (hepcidin)	Thalassaemia (non-transfusion dependent)	Phase 2	Sapablursen (TMPRSS6)	
Iron metabolism (hepcidin)	Thalassaemia	Preclinical	Erythroferrone antibody	
Increasing fetal haemoglobin production	Diamond Blackfan Anaemia	Phase 2 completed	Sirolimus (rapamycin)	
Increasing fetal haemoglobin production	Sickle cell disease	Phase 1b	FTX-6058	

[1] *Cut-off date: 10 November 2022*

Increasing fetal haemoglobin production	Sickle cell disease and thalassaemia	Preclinical	Combination of Simvastatin and Romidepsin	
Increasing fetal haemoglobin production	Thalassaemia (non-transfusion dependent)	Phase 1b	Benserazide	
Polymerization inhibitor	Sickle cell disease	Phase 3	Inclacumab	
Polymerization inhibitor	Sickle cell disease	Phase 2/3	GBT601	
Spleen tyrosine kinase (SYK) inhibitors	wAIHA	Phase 3	FORWARD; Fostamatinib	
Proteasome inhibitor	wAIHA	Phase 2	Bortezomib	With dexamethasone and dexamethasone plus rituximab
PI3Kδinhibitor	wAIHA	Phase 3	PATHWAY; Parsaclisib	Phosphoinositide 3-kinases (PI3Ks) enzymes fundamental in the regulation of cell metabolism, proliferation and survival
Anti-FcRn	wAIHA	Phase 2/3	ENERGY; Nipocalimab	neonatal fragment crystallizable (Fc) receptor (FcRn) functions as a recycling mechanism to prevent degradation and extend the half-life of IgG and albumin in the circulation.
E-selectin antagonist	Sickle cell disease	Phase 3	Rivipansel	
Thrombopoietin receptor agonist	Diamond Blackfan Anaemia (non-steroid respondent), Also used in myelodysplastic syndrome, enhancing iron chelation in thalassaemia, aplastic anaemia	Phase 1/2	eltrombopag	NCT04269889
Gene addition	Diamond Blackfan Anaemia	Preclinical		
Gene addition	Fanconi Anaemia	Phase 2	RP-L102	
Gene addition	Pyruvate kinase deficiency	Phase 1	RP-L301	NCT04105166 Est completion March 2023
Gene addition	Sickle cell disease	Phase 1/2	Lovo-cel	NCT02140554
Gene editing	Sickle cell disease	Phase 1/2	MOMENTUM; ARU-1801	
Gene editing	Sickle cell disease	Phase 1/2	PRECIZN-1; BIVV003	
Gene editing	Sickle cell disease	Phase 1/2	CEDAR; GPH101	
Gene editing	Sickle cell disease	Phase 1/2	RUBY; EDIT-301	
Gene editing	Sickle cell disease	Phase 3	exa-cel	
Gene editing	Thalassaemia	Phase 3	exa-cel	
Gene editing	Thalassaemia	Phase 1/2	EDITHAL; EDIT-301	

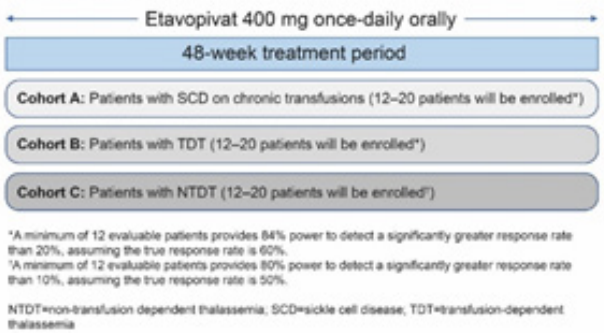
- **Mitapivat,** an oral small molecule that activates red blood cell pyruvate kinase, a key enzyme involved in converting sugar molecules into energy for the cells. Already approved for adults with PKD (see above), investigations are ongoing for its efficacy and safety in other rare anaemias, including thalassaemia and sickle cell disease.

  A phase 2 clinical trial has been completed in non-transfusion-dependent (NTD) α-thalassaemia (HbH disease; 5 patients) or NTD β-thalassaemia (15 patients). The trial resulted in 16 of 20 patients demonstrating a haemoglobin response with no serious side effects. These results supported the continued investigation of mitapivat for the treatment of both α-thalassaemia and β-thalassaemia[2]. Likewise a phase 2 trial indicates safety and efficacy of mitapivat, in sickle cell disease[3]. Following these successful early-phase trials, two phase 3 trials of mitapivat in thalassaemia (ENERGIZE and ENERGIZE-T) and a phase 2/3 trial of mitapivat in sickle cell disease (RISE UP) have begun worldwide.

  Promising preclinical studies have additionally been done evaluating mitapivat in hereditary spherocytosis, suggesting potential efficacy in erythrocyte membranopathies as well[4].

- **Etavopivat (FT-4202)** is an orally administered, activator of erythrocyte pyruvate kinase-R (PKR). It is in clinical development for the treatment of sickle cell disease and other hemoglobin disorders. A human phase 1 trial in SCD has been completed[5], showing improvements in red blood cell oxygenation and deformability, increasing the lifespan of RBCs and decreasing haemolysis[6]. This has opened up the way for phase 2 which will include studies in thalassaemia (TDT and NTDT) and low risk myelodysplasia. A Phase 2/3 study (Hibiscus Study) in SCD is ongoing and will lead to the phase 3 portion of the trial.

Figure 1. Design of Phase 2 Study to assess etavopivat in SCD and Thalassaemia (TDT and NTDT).[7]



- **Hepcidin related therapies:** Hepcidin is hormone with a major role in the regulation of iron regulation in the body. In thalassaemia and other iron loading anaemias, hepcidin is significantly depressed and by increasing the level beneficial effects are expected in iron metabolism and in erythropoiesis (red cell production), which is ineffective in thalassaemia and other anaemias, so restoration of levels could improve ineffective erythropoiesis. However, the use of hepcidin and hepcidin-like substances has failed, thus far, to prove efficacy in human trials.
  - Other approaches to enhance hepcidin action have been pursued and inhibiting substances that regulate its function is now an approach that is being tried. For example an enzyme 'transmembrane serine protease (Sapablursen previously known as TMPRSS6) is a potent inhibitor of erythroferrone which acts a hepcidin suppressor, and is a target for the treatment of β-thalassaemia, polycythemia vera[8] and other iron-loading anaemias associated with low hepcidin levels[9]. Likewise erythroferrone antibody is under development.
  - **Apotransferrin** has been shown to upregulate hepcidin, and this has led to a phase 2 trial of intravenous apotransferrin every 2 weeks in patients with β-thalassaemia intermedia that seeks to raise hemoglobin and reduce transfusion requirements.
  - A hepcidin-like drug **Rusfertide (PTG-300)** is in phase 2 trial for polycythemia vera.

- **Substances which increase HbF (fetal haemoglobin) production:** These will benefit the thalassaemia syndromes since they will reduce the globin chain imbalance, which is the basis of ineffective red cell production. They will also reduce the relative proportion of HbS and so potentially reduce sickling in the sickle cell syndromes.
  - One example in advanced clinical trials is **FTX-6058** an oral drug, which is being developed for sickle cell disease and thalassaemia.
  - Another substance in clinical use for many years to treat Parkinson's disease, **benserazide**, has been shown to increase HbF and so a phase 1b clinical trial has been initiated to identify doses that safely increase F-cells and HbF/cell initially in patients with δ-thalassaemia intermedia, with expansion to patients with SCD if indicated[10].
  - **Simvastatin** and **Romidepsin** in combination have been shown to induce 3-fold increase HbF, in both thalassaemia and sickle cell, with few side effects and can reduce the need for blood transfusion[11, 12].

- **Sirolimus** seems to be a promising option especially in refractory cases of pure red aplasia (Diamond Blackfan Anaemia)[13]. Sirolimus is also a HbF inducer.

- **Inclacumab** is a novel P-selectin inhibitor (monoclonal antibody) currently in Phase 3 clinical trials to reduce vaso-occlusive crises (VOCs) in sickle cell disease by reducing polymerization of HbS. This is one of a series of new therapies that have been approved or are in trials for this haemoglobin disorder. Another sickle hemoglobin (HbS) polymerization inhibitor in earlier phase trials is **GBT601**; like inlacumab it has already received orphan drug and rare pediatric disease designations by the FDA.

- **Spleen tyrosine kinase (SYK)** inhibitors for the treatment of autoimmune diseases as well as malignancies. Several of this group of substances are under investigation for the treatment of autoimmune haemolytic anaemia with acceptable tolerability and safety. For example in a phase 2, clinical study, **fostamatinib** markedly improved Hgb levels in 46% of patients with wAIHA (warm antibody), while adverse events were manageable[14]. Promising results of the phase 3 trial are being analyzed[15].

- **Bortezomib**, in combination with dexamethazone reduces plasma cells responsible for autoantibodies in autoimmune haemolytic anaemia; in a report of 8 patients with severe multi-refractory wAIHA, 6 out of 8 patients responded, with at least a 2 g/dL of Hb increase from baseline[16].

- **Parsaclisib** reduces B-cell production of anti-erythrocyte autoantibodies. In a phase 2, study parsaclisib was administered to both patients with wAIHA, cold and mixed type AIHA; 20 subjects completed 12 weeks of treatment and 16 patients (64%) responded, and 8 (32%) achieved a complete remission[17].

- **Nipocalimab** is currently in phase 2/3 trials for autoimmune hemolytic anaemia[18]. It is a human monoclonal IgG1 antibody.

- **Rivipansel,** a predominately E-selectin antagonist, was studied in a phase 3 trial involving 320 patients with sickle cell disease, of which 162 were given rivipansel as an intravenous loading dose, followed by up to 14 additional 12-hourly maintenance doses (the rest were given a placebo). The drug was also administered during subsequent vaso-occlusive crises. A reduction of time to readiness for discharge occurred when given at the onset of pain[19] so timing of rivipansel administration appears to be critical in order to achieve accelerated resolution of the crisis.

- **Genetic therapies:** There are two approaches to gene therapy, gene addition (using transduction by a lentiviral vector) and gene editing.

  Gene addition involves harvesting and treating the patient's haematopoietic stem cell and returning them in an autologous transplant procedure. This involves myeloablation conditioning which is the source of the adverse effects of the procedure.

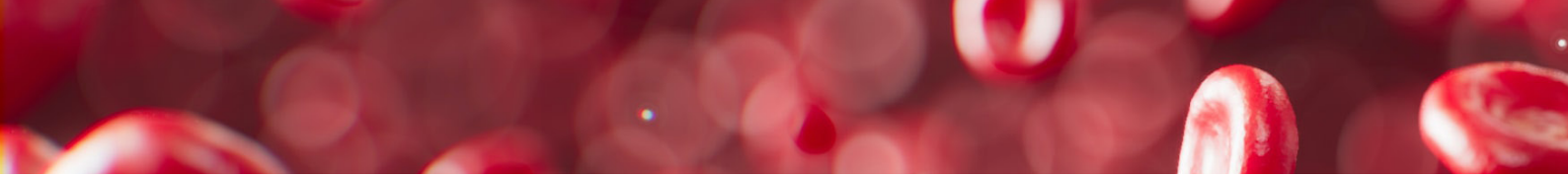
  - One method of **gene addition** in thalassaemia already has received FDA approval (Zynteglo® - betibeglogene autotemcel, or beti-cel)[20] for paediatric and adult patients. Zynteglo® can only be administered at Qualified Treatment Centers (QTCs) in the USA, which are carefully selected based on their expertise in areas such as transplant, cell and gene therapy, and are trained to administer Zynteglo® . The first wave of QTCs trained and activated in September 2022, in anticipation of initiating first patient apheresis in the fourth quarter.

  More information on how to access gene therapy for thalassaemia in the USA is available at www.mybluebirdsupport.com

  The phase 1/2 gene addition therapy clinical trial for patients living with sickle cell disease (lovo-cel) aged 18 and above continues. Preliminary results have shown no vaso-occlusive crises, near-normal haemolysis makrkers and normalization of total haemoglobin up to 24 months after infusion[21].

  Gene therapy in pyruvate kinase efficiency, utilizing lentiviral transduction of autologous hematopoietic stem and progenitor cells (HSPCs), has yielded results in two initial adult patients suggesting potential for extensive correction of anaemia.

  The use of gene addition therapy in Diamond-Blackfan and Fanconi's Anaemia is also being explored.



- **Gene editing** involving DNA manipulation is a potential therapeutic approach to congenital anaemias. In haemoglobin disorders (thalassaemia and sickle cell disease) one main objective of gene editing is the silencing of a gene that controls the production of HbF (known as BCL11A); this allows the production of fetal haemoglobin in children and adults, reducing globin chain imbalance. An advanced phase 3 clinical trial in thalassaemia for exa-cel is ongoing, with promising results; 42/44 patients with TDT were transfusion-free with follow-up ranging between 1.2 – 37.2 months after infusion[22]. The EDITHAL phase 1/2 study (EDIT-301) has begun in 2022[23]. Preliminary data from the phase 1/2 MOMENTUM (ARU-1801) study in sickle cell disease has been positive, using reduced-intensity conditioning with less toxicity relative to myeloablative approaches[24]. Data from the PRECIZN-1 (BIVV003) trial (preliminary phase 1/2 proof of concept study)[25] and CEDAR (GPH101) trial (phase 1/2)[26] have also been positive, whereas the RUBY (EDIT-301) trial (phase 1/2) has begun in 2022[27]. The phase 3 clinical trial to assess exa-cel in sickle cell disease has demonstrated particular positive results (all 31 enrolled patients had no vaso-occlusive crises for up to 32 months after treatment and a high proportion of HbF)[28]. Apart from these conditions, Fanconi's Anaemia is also a candidate although clinical trials are in early stages phase 2[29].

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