CT Application(s) Summary Report

- **Protocol Title:** An Open-Label, Multi-Centre, Rollover Study to Characterise Long-Term Safety and Efficacy of Etavopivat in Adults, Adolescents and Children who Have Sickle Cell Disease or Thalassemia and Have Completed a Treatment Period in an Etavopivat Study (FLORAL)
- **Protocol Code Number:** NN7535-7822
- **Public Registry Number:** 2024-510805-27
- **Version:** 1.0
- **Date:** 03-May-2024

- **Investigational Medicinal Product being Tested:**

Biological ☐ **Pharmaceutical** ■ **Innovative** ☐

Herbal Medicine ☐ **Medical Device** ☐

- **Sponsor:** Novo Nordisk A/S

- **Indication:** Sickle Cell Disease and Thalassemia

- **Investigator's Brochure (IB)**

Version: Edition 7
Date: 25 February 2025

- **Name of all Sites:**
  1- Kasr Al Aini Hospital, Cairo University,
  2- Abu El Rich Children Hospital, Cairo University,
  3- Zagazig University Hospital,
  4- Alexandria University CRC, (2 sites)
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- **Summary of Pre-Clinical Studies**

Etavopivat is an orally bioavailable, small-molecule activator of red blood cell pyruvate kinase isozyme (PKR). The investigational medicinal product (IMP) is being developed for the treatment of inherited haemoglobinopathies, such as sickle cell disease (SCD) and thalassaemia as well as a treatment of myelodysplastic syndrome-associated (MDS-associated) anaemia.

➢ **Physical, Chemical, and Pharmaceutical Properties and Formulations**

Etavopivat is a synthetic small molecule that is the active pharmacological ingredient (API) in oral etavopivat tablets. Etavopivat tablets for adults and adolescents are presented in 200 mg strength. The tablets are film-coated and contain etavopivat amorphous solid dispersion with compendial excipients.

A granule formulation of 2 mg strength has been developed for paediatric patients below 12 years of age. These are film-coated, round-shaped granules/mini-tablets, with a diameter of 2 mm. They contain etavopivat amorphous spray dried dispersion (SDD) and compendial excipients. Granules are packaged into foil stick packs as 20 mg and 100 mg strengths. The placebo tablet's appearance is identical to the etavopivat tablets.

➢ **Nonclinical Studies**

- **Pharmacology**

In vitro enzymatic and cellular assays indicate that etavopivat is an allosteric activator of PKR. PKR exists in both a dimeric and tetrameric state, but functions most efficiently as a tetramer. etavopivat stabilizes the tetrameric form of PKR, thereby lowering the Michaelis-Menten constant (Km) for its substrate, phosphoenolpyruvate (PEP). etavopivat is a potent and effective activator of PKR in both human and mouse red blood cells (RBCs). The potential clinical consequence of PKR activation was demonstrated in cellular assays with RBCs from patients with SCD in which etavopivat increased haemoglobin-oxygen (Hb-O2) affinity and reduced sickling under severe hypoxic conditions. The pharmacological activity contribution (PKR activity) of the O-glucuronide metabolite of etavopivat, M633/1, is considered negligible with an EC50 of 41.8 µM.

The in vivo pharmacology studies for etavopivat in mice demonstrated the pharmacokinetic (PK)/pharmacodynamic (PD) relationship of etavopivat exposure and PKR activation in wild-type (WT) mice as well as in a murine model with the SCD phenotype. In the murine model of SCD, 2-week etavopivat exposure was well tolerated, and a beneficial biological effect was demonstrated. These effects included decreased 2,3-diphosphoglycerate (2,3-DPG), increased adenosine triphosphate (ATP), decreased numbers of irreversibly sickled cells, increased RBC half-life, increased haemoglobin (Hb) levels, increased RBC numbers, increased haematocrit (HCT), improved Hb-O2 affinity, reduced deoxygenation-induced cellular deformability, and decreased spleen weight. Taken together, the murine data support exposure-related therapeutic benefits of etavopivat for the treatment of SCD.

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The PK/PD relationship between etavopivat exposure and changes in 2,3-DPG and ATP baseline levels in blood was determined in cynomolgus monkeys following a single dose of etavopivat and after daily dosing for 5 days. The effects of etavopivat on 2,3-DPG and ATP levels in RBCs were evaluated in the 28-day Good Laboratory Practice (GLP) toxicity studies performed in rats and monkeys, which indicate that the exposures of etavopivat required for a maximum PD effect were below the exposures that defined the no observed adverse effect level (NOAEL) in these 2 species.

etavopivat had no effect on steroidogenesis at doses <20 µM, and no meaningful activity of etavopivat was observed against a broad range of receptors, ion channels, transporters, and kinases at concentrations up to 10 µM. In the in vitro GLP electrophysiological study, the estimated half maximal inhibitory concentration (IC50) of etavopivat on the human ether-à-go-go-related gene (hERG) potassium current was >300 µM.

In vivo safety pharmacology studies found no etavopivat-related effects on central nervous system (CNS) parameters or respiratory function in rats at doses of up to 350 mg/kg. In a cardiovascular study in cynomolgus monkeys, a transient increase in mean heart rate (HR) was recorded after dosing at the 350 and 550 mg/kg dose levels. The changes were considered non-adverse. HR values remained within the normal physiological range, however, a potential effect of etavopivat could not be excluded. There were no other changes in any of the cardiovascular parameters measured.

The PD response to etavopivat in relation to PKR was demonstrated in vitro and in preclinical models, providing valuable evidence of target modulation and disease-modifying behavior which supports the rationale for subsequent clinical studies.

- **Absorption, Distribution, Metabolism and Excretion**

Etavopivat PK was evaluated after intravenous (IV) administration and after oral (per os [PO]) administration in mice, rats, and monkeys. etavopivat demonstrated a low to moderate clearance, a short half-life, high oral bioavailability (F_{oral}) (≥50% F_{oral}), and moderate volume of distribution across all species tested. etavopivat is moderately bound to plasma proteins in humans (69%) closely matching that of rats (81%) and monkeys (74%), the selected safety species. etavopivat has a high membrane permeability in Caco-2 cells (apparent permeability [P_{app}]($_{A\ B}$) = 5.5 x 10–6 cm/s) consistent with good oral absorption in humans. etavopivat is *in vitro* metabolized by oxidation through the cytochrome P450 (CYP) enzymes CYP3A4, CYP3A5 and CYP2C9, and by glucuronidation that is mainly through uridine diphosphate glucuronosyltransferases (UGT)2B7 and to a lesser extent UGT2B15 and UGT1A9. The major O-glucuronide metabolite of etavopivat (M633/1) was observed in rat and monkey plasma but the exposure was less compared to human exposure at steady state with ratios of 0.01 and 0.04, respectively.

The overall risk of clinically relevant drug-drug interactions (DDIs) with etavopivat is predicted to be low. No significant reversible or time-dependent inhibition of the drug-metabolizing enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 by etavopivat was observed at concentrations up to 50 µM. For CYP3A4, less than 50% inhibition was observed at the solubility-limited concentration of 225 µM, thus no IC_{50} value

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could be calculated. etavopivat did not significantly induce the expression of CYP1A2, 2B6 and 3A4. Analysis of etavopivat in MDCKII/MDR1 cells overexpressing P-glycoprotein (P-gp) indicated that etavopivat is a substrate for P-gp. Under the investigated condition, etavopivat was found not to be a substrate of any of the common transporters: breast cancer resistance protein (BCRP), organic anion transporters (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, multidrug and toxin extrusion protein (MATE)1 and MATE2-K. *In vitro*, etavopivat inhibits UGT1A3, UGT2B7, UGT2B15 and UGT2B17 with IC50 of 68.9, 8.71, 59.2 and 38.2 µM, respectively. No relevant inhibition of UGT1A1, UGT1A4, UGT1A6 and UGT1A9 was observed up to 100 µM. The risk of etavopivat being a clinically relevant inhibitor of any of the transporters BCRP, P-gp, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1 and MATE2-K is considered low. The DDI risk of the O-glucuronide metabolite of etavopivat, M633/1, is considered low based on *in vitro* assessments for CYP inhibition, UGT inhibition, and transporter inhibition.

- **Toxicology**

Nonclinical data supporting the safety of human studies are provided principally by definitive repeat-dose toxicity and toxicokinetic (TK) studies with durations up to 26 weeks in rats and 39 weeks in cynomolgus monkeys, pivotal embryo-fetal development (EFD) studies performed in rats and rabbits, a pre- and postnatal development study in rats, juvenile toxicity studies in juvenile rats and carcinogenicity studies in transgenic mice for 26 weeks and 2 years in rats.

- In the definitive 4-week toxicity study conducted in rats, etavopivat was well tolerated with no etavopivat-related clinical or anatomic pathology effects; thus, the NOAEL was the highest dose of 350 mg/kg/dose (700 mg/kg/day).
- In the 13-week toxicity study in the rat, etavopivat was well tolerated and etavopivat-related adverse microscopic findings were limited to inflammation and/or necrosis in the renal papillae of females administered the highest dose of 700 mg/kg/day. These microscopic findings were considered secondary to the presence of etavopivat-related urine crystals of unknown composition. Females administered ≥100 mg/kg/day and males administered ≥300 mg/kg/day had urine crystals. The microscopic findings in the renal papillae and urinalysis findings were reversible. The NOAEL was 350 mg/kg/dose (700 mg/kg/day) in males and 150 mg/kg/dose (300 mg/kg/day) in females, which is associated with a ≥130-fold exposure multiple versus the free area under the concentration time curve (AUC) determined at the clinical dose of 400 mg once daily (QD) which is the proposed dose for adolescents (≥12 years of age) and adults.
- In the 26-week toxicity study in the rat, the rats were administered etavopivat by oral gavage administration of 25, 100, or 350 (males) / 250 (females) mg/kg/dose twice daily (BID) (50, 200, or 700 [males] / 500 [females] mg/kg/day). All doses were clinically well tolerated, with no etavopivat-related adverse clinical signs or adverse effects on body weight or food consumption. etavopivat-related effects on urinalysis consisted of urine crystals in females administered ≥200 mg/kg/day, which was reversible,

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and mildly higher urine osmolality in males administered ≥200 mg/kg/day and females administered 500 mg/kg/day (recovery was not assessed during the recovery phase). The urinary crystals were assessed to be primarily comprised of etavopivat and were the cause of the macroscopic and microscopic findings in the urinary bladder and kidney. The etavopivat-related microscopic findings in the kidney of terminal sacrifice animals included crystals and/or associated pyelonephritis in animals administered ≥200 mg/kg/day and erosion/ulcer in the glandular stomach of animals administered ≥50 mg/kg/day. The stomach precipitates were analyzed to be primarily comprised of etavopivat. These findings were minimal and reversible and therefore considered overall non-adverse, with the exception of males administered 700 mg/kg/day, where pyelonephritis in combination with a higher incidence and severity of erosion/ulcer in the glandular stomach was considered minimally adverse. These findings did not persist to recovery sacrifice, suggesting complete reversal. The NOAEL for toxicity was 200 mg/kg/day in males and 500 mg/kg/day in females which was associated with a 39- and 160-fold exposure multiple compared with the free AUC determined at the clinical dose of 400 mg QD, respectively.

- The 26-week toxicity study in rats did also evaluate the potential effects of etavopivat on mating, male fertility and on early EFD (number of corpora lutea, implantations, viable fetuses, and pre- and post-implantation loss on gestation day [GD] 13). No etavopivat-related effects on mating, fertility and early EFD of the offspring of etavopivat-treated male rats were observed when paired with naïve females. The NOAEL for mating and fertility for male rats was 700 mg/kg/day, associated with a 64-fold exposure multiple compared with the free AUC determined at the clinical dose of 400 mg QD.
- In the 4-, 13- and 39-week toxicity studies in cynomolgus monkeys, animals were dosed up to 550 mg/kg/day etavopivat QD. All the doses were well tolerated without any related adverse effects in any study. The NOAEL across the 3 studies was 550 mg/kg/day which is associated with a 37-fold exposure multiple compared with the free AUC determined at the clinical dose of 400 mg QD.
- Pivotal rat combined female fertility, EFD and rabbit EFD studies have been conducted with etavopivat. No adverse effects on fertility and EFD were noted in these studies. In the pivotal pre- and post-natal development study in rats, etavopivat was administered during the period of organogenesis and continuing until weaning and no adverse effects on pup growth and development, and reproductive performance were observed up to the highest dose of 250 mg/kg BID (68 times the maximum recommended human dose, based on AUC).
- The juvenile toxicity studies showed no etavopivat-related adverse effects up to the highest dose of 100 mg/kg/day, which is associated with a 23-fold exposure multiple compared with the free AUC at the clinical (adult) dose of 400 mg QD. The dosing duration from postnatal day (PND) 14 to 42 covers the intended pediatric age range from 6 months to 18 years.
- Etavopivat was not mutagenic in the bacterial reverse mutation (Ames) assay and was not genotoxic in the *in vitro* human peripheral blood lymphocyte (HPBL) micronucleus and *in vivo* rat micronucleus

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assays. etavopivat was not phototoxic in a neutral red-uptake phototoxicity assay conducted in BALB/c3T3 mouse fibroblasts.

- In the carcinogenicity studies in transgenic rasH2 mice, etavopivat was administered up to 700 mg/kg/day for up to 26 weeks resulting in an AUC value of 476,000 ng*hr/mL. etavopivat was clinically well tolerated and no effect on survival or evidence of any carcinogenic potential was noted in animals administered up to the highest tested dose. This exposure is associated with a >75-fold exposure multiple compared with the free AUC determined at the clinical dose of 400 mg QD.
- In the 2-year carcinogenicity study in rats, daily administration of 15, 50 or 125 mg/kg/day etavopivat by oral gavage to male rats and 10, 30, or 85 mg/kg/day etavopivat to female rats did not result in an etavopivat-related effect on survival or statistically significant increased neoplasia. The neoplastic no observed effect level (NOEL) for etavopivat was set to 125 mg/kg/day for males and 85 mg/kg/day for females. The corresponding exposure ratios were for males 38 times and for females 26 times the human exposure of 400 mg QD based on the free AUC.

- **Nonclinical Safety**

Overall, the animal toxicity profile of etavopivat indicates that the rat was the sensitive nonclinical species and key affected organs were kidney and gastrointestinal (GI) system. The findings related to kidney and GI effects were reversible.

- Etavopivat was well tolerated in juvenile rats dosed up to 4 weeks spanning PND 14 to 42; this duration covers the intended pediatric age range from 6 months to 18 years and provides preclinical support for the safety of etavopivat in pediatric patients.
- Etavopivat was not embryotoxic or teratogenic with no effects on mating and fertility, and etavopivat was not genotoxic or phototoxic in the respective nonclinical studies.
- Etavopivat was not carcinogenic in transgenic rasH2 mice dosed up to 700 mg/kg/day when given orally twice daily for 26 weeks, and no carcinogenic potential of etavopivat was observed in a 104-week carcinogenicity study in rats, following the administration of up to 125 mg/kg/day in males and up to 85 mg/kg/day in females, the highest dose levels tested.

- **Nonclinical Assessment**

Based on the submitted nonclinical data, the overall preclinical development programme for etavopivat is considered adequate to support Phase 3 clinical development and is compliant with the relevant requirements of ICH M3(R2) and applicable ICH safety guidelines, including ICH S7A/S7B, S5(R3), S6 (as applicable), and S1 for carcinogenicity. The nonclinical package is comprehensive and appropriate for the intended chronic use in adult, adolescent, and pediatric populations.

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Primary pharmacology studies adequately characterize the mechanism of action of etavopivat as an allosteric activator of red blood cell pyruvate kinase (PKR), with consistent demonstration of target engagement in vitro and in vivo. The pharmacological relevance to the proposed indications is supported by data in disease-relevant cellular systems and in a murine model of sickle cell disease, where exposure-dependent effects on key biomarkers (e.g. 2,3-DPG and ATP), red blood cell survival, and haematological parameters were observed. These findings support a disease-modifying mode of action and provide a biologically plausible rationale for clinical efficacy. The contribution of the major circulating metabolite (M633/1) to pharmacological activity appears negligible.

Secondary pharmacology and safety pharmacology evaluations did not identify clinically relevant off-target activities. In vitro and in vivo safety pharmacology studies addressing cardiovascular, respiratory, and central nervous system functions were conducted in accordance with ICH S7A/S7B. Aside from a transient, non-adverse increase in heart rate at high doses in monkeys, no adverse effects were observed, and the overall safety pharmacology profile is considered acceptable.

- The ADME programme is adequate and well characterized. etavopivat demonstrates favorable oral bioavailability across species, moderate clearance, and predictable distribution. Plasma protein binding is comparable between humans and the selected nonclinical species. Metabolic pathways have been appropriately characterized, with CYP- and UGT-mediated metabolism identified. The major human metabolite was present at lower exposure levels in the toxicology species, and its pharmacological and DDI potential were adequately assessed. Based on the submitted in vitro data, the risk of clinically relevant CYP- or transporter-mediated drug–drug interactions is considered low.
- **Repeat-dose toxicity studies** of appropriate duration were conducted in rats and cynomolgus monkeys, with exposures exceeding those anticipated at the proposed clinical dose. The rat was identified as the more sensitive species, with kidney and gastrointestinal tract effects observed at high doses, largely attributable to precipitation and crystal formation of the parent compound. These findings were generally reversible and exposure-dependent. In monkeys, etavopivat was well tolerated up to the highest tested doses, with no adverse findings identified. The derived NOAELs in both species provide adequate safety margins relative to human exposure at the proposed Phase 3 dose.
- The reproductive and developmental toxicity programme is complete and consistent with ICH S5(R3). No adverse effects on fertility, embryo-fetal development, or pre- and post-natal development were observed in rats or rabbits at exposures substantially exceeding clinical exposure. Juvenile toxicity studies in rats, covering postnatal development relevant to the intended pediatric population, did not reveal any etavopivat-related adverse findings and are considered supportive of pediatric use.
- Genotoxicity studies were negative, and phototoxicity risk was excluded. Carcinogenicity was appropriately assessed in transgenic mice and in a 2-year rat study, with no evidence of carcinogenic potential observed at exposure multiples considered adequate for chronic clinical use.

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In conclusion, the submitted nonclinical data are considered sufficient and appropriate to support Phase 3 clinical development of etavopivat. No nonclinical safety concerns have been identified that would preclude long-term administration in the proposed adult, adolescent, or pediatric patient populations, provided that renal and gastrointestinal findings observed at high exposures are appropriately monitored in the clinical setting.

- **Summary of Previous Clinical Studies:**

1. Effects in humans

1.1. Pharmacokinetics and Product Metabolism in Humans

- Following oral administration in healthy participants and in patients with SCD, etavopivat was rapidly absorbed, with plasma exposure generally increasing with increasing dose (4202-HVS-101). Metabolite profiling confirmed that etavopivat was extensively metabolised in humans with >18 metabolites detected (4202-HVS-103). M633/1, a glucuronide of etavopivat, was the most abundant circulating entity, accounting for 65.6% of the administered dose. The major elimination pathway for metabolites of etavopivat is in the feces. The most abundant metabolite in feces was M475/1, accounting for 9.86% of the dose. The most abundant metabolite in urine was M633/1 accounting for 9.33% of the dose. Urine is considered a minor excretion route for etavopivat in humans (4202-HVS-103).
- Oral administration of etavopivat as either 2 x 100 mg tablets or 1 x 200 mg tablets resulted in similar plasma PK profiles (4202-HVS-102). The etavopivat granule formulation administered in a 400 mg dose and as 2 x 200 mg etavopivat tablets had similar PK profiles but could not be considered bioequivalent (4202-HVS-105). There was no definitive food effect observed for the etavopivat Phase 1 tablet formulation (4202-HVS-101). Soft food increased peak etavopivat exposure by 46% following administration of the granule but did not affect total etavopivat exposure (4202-HVS-105).
- Co-administration of etavopivat (400 mg) with a strong CYP34A/P-gp inhibitor (itraconazole) resulted in a 1.8-fold increase in AUC and a 1.1-fold increase in maximum observed plasma concentration (Cmax) (4202-HVS-104). This exposure was lower than that observed with daily dosing of etavopivat 600 mg QD for 14 days which was a well-tolerated dose in patients with SCD. The co-administration of
- etavopivat with a strong CYP3A4/P-gp inducer (phenytoin) resulted in a 2.7-fold decrease in AUC and 3.4-fold decrease in Cmax (4202-HVS-104). It is concluded therefore, that moderate/strong CYP3A4/P-gp inhibitors should not be restricted, while strong CYP3A4/P-gp inducers should be restricted in clinical studies with etavopivat.

1.2. Efficacy

The clinical activity of etavopivat has been evaluated in a randomized, placebo-controlled, double blind, SAD and MAD study in healthy participants and in patients with SCD (4202-HVS-101) and in a

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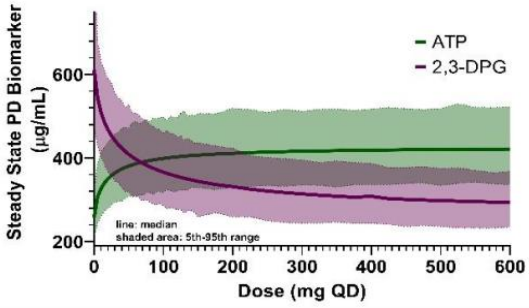
randomized, placebo-controlled, double-blind, multi-center Phase 2/3 study in participants with SCD (4202-HEM-301, dose determination portion). No efficacy data are yet available for etavopivat in patients with thalassaemia or MDS.

1.2.1. Pharmacodynamics

1.2.1.1. Healthy Participants

- In study 4202-HVS-101, blood 2,3-DPG levels decreased after single and multiple doses of etavopivat, and this decrease was sustained >1 day following the last dose. Blood ATP levels increased after repeated dosing with etavopivat and the increase was sustained >3 days following the last dose. Similarly, increased Hb-O2 affinity was observed following single and multiple doses at all etavopivat dose levels tested.
- PK/PD modelling was used to predict PD responses in HV RBCs. These analyses indicated that the maximal responses for ATP and 2,3-DPG would be achieved with etavopivat QD doses of ≥150 and 400 mg, respectively.

Predicted PD response in HV RBCs



Abbreviations: ATP = adenosine triphosphate; HV = healthy volunteers; PD = pharmacodynamic; QD = once daily; RBCs = red blood cells; 2,3-DPG = 2,3-diphosphoglycerate.

1.2.1.2. Patients with SCD

- Consistent with the expected PD effects of PKR activation, rapid and sustained pharmacological activity was observed in patients with SCD. More specifically, 24 hours after a single 700-mg dose of etavopivat, blood concentrations of ATP increased by 30% and 2,3-DPG blood concentrations decreased by 26%. For patients with SCD receiving 14-day administration of etavopivat, 2,3-DPG levels decreased within 24 hours (p=0.031), while ATP levels increased through to treatment day 7 (p=0.031). Both effects were sustained through the 14-day dosing period.
- Notably, despite the increased exposure observed with etavopivat 600 mg QD vs. 300 mg QD, PD responses (decreased 2,3-DPG and increased ATP) were comparable across both 14-day SCD cohorts. This confirmed findings from previous studies in healthy RBCs which predicted that maximum PD activity would be provided in etavopivat doses ≥400 mg QD. For the 12-week OLE cohort, durable PD

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responses (decreased 2,3-DPG and increased ATP) were observed over 12 weeks of treatment with a gradual return to baseline after 4 weeks of washout.

- In patients with SCD who received a single dose (700 mg) of etavopivat, analysis of change from baseline showed improved haematologic parameters 24 hours after dosing.25 More specifically, a single dose of etavopivat resulted in a mean increase in Hb levels of 0.5 g/dL (range: 0.3 to 0.9) compared to a mean decrease of -0.4 g/dL (range: -0.5 to -0.3) in patients who received placebo. Decreased LDH was also observed in etavopivat-treated patients 72 hours after etavopivat dosing. Together, these results suggest that a sustained 2,3-DPG and ATP response may be required for optimal benefit.
- For patients with SCD who received 14 days of etavopivat QD, 73% of patients (11/15) achieved an Hb response >1 g/dL over baseline (mean increase 1.2 g/dL; $p<0.002$). At the end of treatment (EOT) visit, 73% (8/11) of these patients had a best Hb >1 g/dL. Notably, 1 week after etavopivat discontinuation, 55% (6/11) had a Hb >0.5 g/dL over baseline. In addition, all evaluated patients (15/15) showed a decrease in absolute reticulocytes relative to baseline at EOT (mean reduction 47%; $p<0.001$). At EOT, 73% (11/15) had decreased LDH levels relative to baseline (mean reduction 19%; $p<0.07$), and 93% (14/15) had decreased indirect bilirubin levels relative to baseline (mean reduction 38%; $p<0.002$).
- Patients with SCD who received etavopivat daily for up to 12 weeks (OLE cohort) showed sustained improvements to haematologic and haemolytic parameters. More specifically, 73% (11/15) of patients who received etavopivat 400 mg QD for at least 2 weeks showed an increase in Hb >1 g/dL, with sustained responses throughout the treatment period. Similar to results for the 14-day cohorts, a significant and sustained decrease in absolute reticulocytes, indirect bilirubin, and LDH was noted by 2 weeks, with sustained responses throughout the treatment period.

Significant and sustained improvements in haematologic and haemolytic parameters in patients receiving up to 12 Weeks of etavopivat (400 mg QD)

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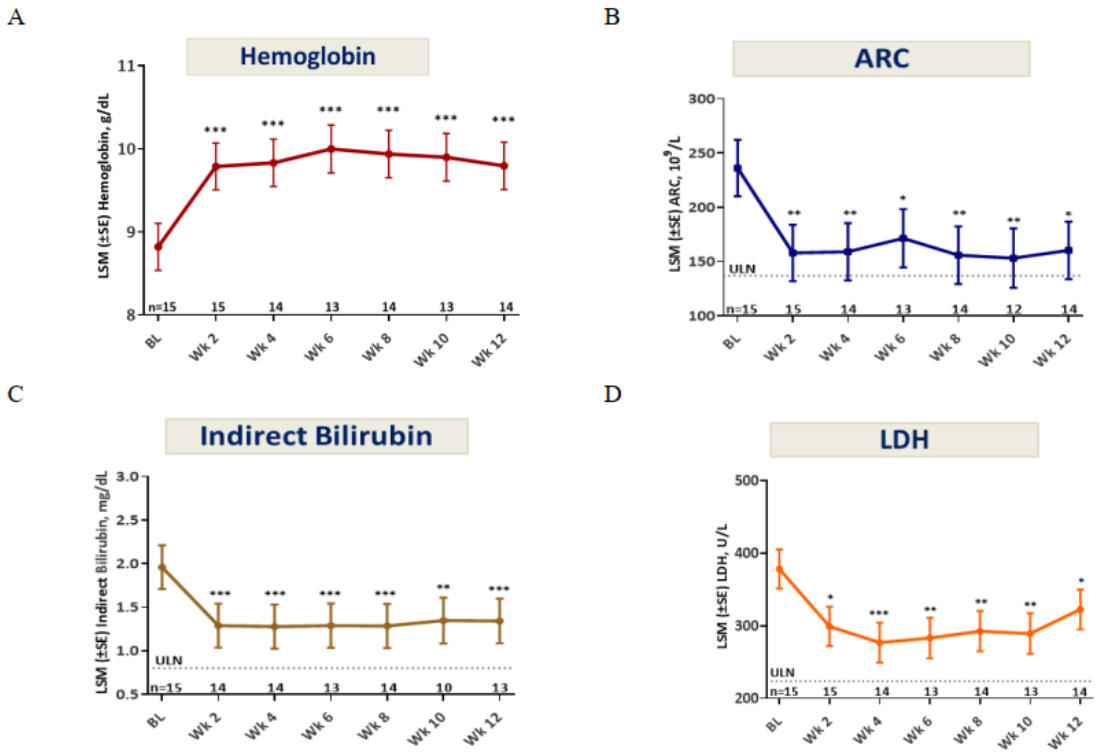

Note: LSM values presented are estimated from a mixed model repeated measures analysis. *p<0.05, **p<0.001, or ***p<0.0001 vs BL.

Abbreviations: ARC = absolute reticulocyte count; BL = baseline; LDH = lactate dehydrogenase; LSM = least squares mean; QD = once daily; SE = standard error; ULN = upper limit of normal; Wk = week.

A decreasing trend in VOCs was observed with etavopivat treatment for up to 12 weeks. Compared with prior history, the rate of VOCs resulting in hospitalisation was lower (68% reduction) in 2-week and 12-week treatment cohorts.

Decreasing trend in VOCs observed with etavopivat QD for up to 12 weeks

Cohort	N	Prior history	Once daily etavopivat on-treatment	
		Annualised VOC[a] rate (no. events)	Annualised VOC[b] rate (no. events)	Exposure duration (patient years)
Etavopivat 2-week cohorts	16	0.88 (13)	0.00 (0)	0.61
Etavopivat 12-week cohort	15	0.93 (13)	0.30 (1[c])	3.32

[a]Includes VOCs resulting in hospitalisation based on chart review and patient recall for up to 12 months prior to study entry. [b]Includes sickle cell anaemia with crisis or ACS requiring hospitalisation, during 12 weeks of etavopivat treatment. [c]VOC precipitated by a COVID infection.

Abbreviations: ACS = acute chest syndrome; COVID = coronovirus-19; N = number; QD = once daily; VOC = vaso-occlusive crisis.

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- Analysis of RBCs from patients with SCD treated with etavopivat 300 or 600 mg QD for 2 weeks showed a comparable increase in PKR activity over baseline. In addition, there was an increase in RBC antioxidant capacity, improved RBC redox potential, and decreased phosphatidylserine expression on the sickle RBC membrane, suggesting improved RBC membrane repair.
- Etavopivat administration increased Hb-O2 affinity (decreased Hb saturation [P50]) both in HV and in patients with SCD. Notably, etavopivat administration normalised P50 values in RBCs of patients with SCD 24-hrs after a single dose or after 14 days of administration. This change in Hb-O2 affinity correlates with the observed 2,3-DPG response.
- Patients with SCD receiving a single dose (700 mg) of etavopivat showed an increased Hb-O2 affinity and decreased deoxy HbS polymerisation rate. In addition, these patients had improved sickle RBC deformability as demonstrated by reductions in PoS and increases in the minimal elongation index. Finally, they showed an improved response to osmotic gradient, indicating improved RBC membrane function.
- A collective analysis of 14 patients with SCD who received etavopivat (300 mg or 600 mg) QD for 14 days showed that etavopivat-treated sickle RBCs had significantly increased Hb-O2 affinity ($p<0.0001$), a significant shift in the PoS as measured by Oxygenscan ($p<0.004$), and significantly improved deformability (EImax) over an oxygen gradient ($p<0.025$) or an osmotic gradient ($p<0.037$). Change from baseline analyses for patients with SCD receiving 14 days of daily etavopivat (300 mg or 600 mg) showed that increased O2 affinity was associated with improvements in RBC PoS and measures of RBC deformability.

1.2.2. Efficacy

The Phase 2 dose determination portion of study 4202-HEM-301 enabled selection of the optimal dose for the Phase 3 at the 12-week IA as well as early evaluation of efficacy of etavopivat treatment compared to placebo after 52 weeks of etavopivat treatment. A total of 7 (11.7%) participants in the study were adolescents. The study was not powered to detect any differences in Hb response or other clinical variables and overall efficacy will be evaluated in the Phase 3 portion of the study.

Efficacy in the Phase 2 dose determination portion was measured by improvement in Hb, annualised VOC rate, changes in measures of haemolysis and changes in QoL measures. Efficacy analyses were performed on the DD population which included all the randomised participants in the dose determination group, based on the Intent to Treat principle. Sensitivity analyses were performed with the PP population, which included all the DD participants who completed the blinded treatment period, received ≥80% of the planned doses of the study drug, and had no major protocol deviations that impacted the efficacy assessment.

Effect on VOCs

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The effect of etavopivat treatment on VOCs was evaluated by the annualised VOC rate as well as time to first VOC across two etavopivat dose treatments and compared to placebo.

The annualised VOC rate, based on adjudicated VOC events, was lower in the etavopivat groups compared to the placebo group; with 1.07 events per year in the etavopivat 200 mg group, 1.06 events per year in the etavopivat 400 mg group, and 1.97 events per year in the placebo group in the DD population. Corresponding numbers for the PP population were 0.66 events per year in the etavopivat 200 mg group, 0.70 events per year in the etavopivat 400 mg group, and 1.77 events per year in the placebo group.

The median time to first VOC was approximately twice as long in the etavopivat groups compared to the placebo group; with 33.6 weeks in the etavopivat 200 mg and 400 mg groups and 16.9 weeks in the placebo group.

Effect on Haemoglobin

The Hb response rate (defined as a change from baseline in Hb >1 g/dL) at week 24 was higher in the etavopivat groups compared to the placebo group, with a 38.1% Hb response rate in the etavopivat 200 mg group, 25.0% in the etavopivat 400 mg group, and 10.5% in the placebo group in the DD population. In the PP population, the rates were 46.2%, 33.3%, and 13.3%, respectively.

Comparison of Haemoglobin Response Rate at Week 24 between etavopivat and Placebo

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	Placebo	Etavopivat 200 mg	Etavopivat 400 mg	Etavopivat Combined
Dose determination population, N	**19**	**21**	**20**	**41**
Patients with Hb response	2	8	5	13
Hb response rate (%)	10.5	38.1	25.0	31.7
Rate difference		27.57	14.47	21.18
(95% CI)		(2.63, 52.51)	(-8.99, 37.94)	(1.35, 41.01)
p-value		0.19	0.66	0.10
Per-protocol population, N	**15**	**13**	**12**	**25**
Patients with Hb response	2	6	4	10
Hb response rate (%)	13.3	46.2	33.3	40.0
Rate difference		32.82	20.00	26.67
(95% CI)		(0.72, 64.92)	(-11.74, 51.74)	(0.88, 52.45)
p-value		0.25	0.68	0.09

Note: Baseline is defined as average of measurements at screening and day 1. Baseline requires both screening and day 1 pre-dose results to be non-missing, otherwise baseline is considered missing. Hb response at week 24 is defined as a change > 1 g/dL between the baseline Hb and the average Hb value at weeks 16, 20 and 24. Response was also adjusted based on the data handling rules for ICEs in Table 2 of the SAP. Hb response rate, rate difference, and 95% CI are unconditional statistics without adjustment of randomisation stratification factors. 95% CIs are calculated using Wald method.

The one-sided p-value is obtained from an exact Cochran-Mantel-Haenszel general association test between the indicated etavopivat group versus placebo and stratified by the randomisation stratification factors.

Abbreviations: CI = confidence interval; Hb = haemoglobin; ICE = intercurrent event; N = number; SAP = statistical analysis plan.

In alignment with Hb response rate, changes in Hb were also observed upon etavopivat treatment. Participants who received either 200 mg or 400 mg QD, showed an increase in Hb within 2 weeks of treatment which was sustained but modulated through the 52 weeks of treatment. At week 52, the estimated treatment difference in Hb change from baseline compared to placebo was 1.0 ([0.3; 1.8]95% CI) g/dL and 0.2 ([-0.6; 1.0]95% CI) g/dL in the etavopivat 200 mg and 400 mg groups, respectively.

Effect on Measures of Haemolysis

Participants receiving etavopivat treatment, either 200 mg or 400 mg, showed a reduction in absolute reticulocyte count (ARC), indirect bilirubin and LDH from baseline compared to placebo. The reduction was evident after 2 weeks of treatment and was sustained but modulated through 52 weeks of treatment.

For ARC, the estimated treatment difference in change from baseline to week 24 compared to placebo was -47.3 ([-103.7; 9.1]95% CI) 109/L and -8.4 ([-66.5; 49.7]95% CI) 109/L in the etavopivat 200 mg and 400 mg groups, respectively.

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For indirect bilirubin, the estimated treatment difference (95% CI) in change from baseline to week 24 compared to placebo was -3.8 ([-13.7; 6.1]95% CI) µmol/L and -3.6 ([-13.9; 6.7]95% CI) µmol/L in the etavopivat 200 mg and 400 mg groups, respectively.

For LDH, the estimated treatment difference (95% CI) in change from baseline to week 24 compared to placebo was -78.1 ([-139.1; -17.2]95% CI) U/L and -57.8 ([-123.5; 7.9]95% CI) U/L in the etavopivat 200 mg and 400 mg groups, respectively.

1.3. Safety

1.3.1. Safety in Healthy Participants

The clinical safety evaluation of etavopivat in healthy participants is based on the results of 5 completed Phase 1 studies.

A total of 40 TEAEs were reported in 26 (28.9%) healthy participants in study 4202-HVS-101, across the SAD, MAD and Food effect (FE) cohorts. Across the other 4 completed Phase 1 studies (4202-HVS-102, 4202-HVS-103, 4202-HVS-104 and 4202-HVS-105), a total of 193 TEAEs were observed in 66 (51.6%) healthy participants.

4202-HVS-101

SAD Cohorts

A total of 7 TEAEs were reported in 6 (18.8%) healthy participants; 5 (20.8%) receiving etavopivat and 1 (12.5%) receiving placebo. TEAEs reported for participants receiving etavopivat included abdominal pain, amylase increased, headache, lipase increased, urethral discharge and ventricular arrhythmia (n=1 [4.2%] for each).

All TEAEs were non-serious, and most were Grade 1 or 2 in severity. However, 1 (4.2%) participant receiving 1000 mg etavopivat had a TEAE of Grade 3 (severe) lipase increased. The event was transient, and the participant was asymptomatic. The back-up sample from the participant was reanalysed independently, and no lipase elevation was observed. Two (2) TEAEs (ventricular arrhythmia and headache) were reported as possibly related to trial product in 2 (8.3%) participants receiving etavopivat. Both events were Grade 1 and resolved without treatment. No participants had dose reductions, dose interruptions or discontinued the trial product due to TEAEs. None had treatment-emergent serious adverse events (TESAEs) or died due to TEAEs.

MAD Cohorts

A total of 31 TEAEs were reported in 18 (37.5%) healthy participants; 15 (41.7%) receiving etavopivat and 3 (25.0%) receiving placebo. The most common TEAE reported was headache; 11 events in 10 (27.8%) participants receiving etavopivat and 3 events in 2 (16.7%) participants receiving placebo. All other TEAEs in participants receiving etavopivat were reported in 1 (2.8%) participant each.

All TEAEs were non-serious and Grade 1 in severity. Six (6) TEAEs in 6 (16.7%) participants receiving etavopivat were reported as possibly related to trial product. All TEAEs resolved without treatment. No participants had dose reductions, dose interruptions or discontinued trial product due to TEAEs.

Food Effect Cohort

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A total of 2 TEAEs were reported in 2 (20.0%) participants in the FE cohort; 1 (10.0%) participant reported skin abrasion in the fasted-fed condition and 1 (10.0%) participant reported rhinitis in the fed-fasted condition.
All TEAEs were non-serious and Grade 1 in severity. No TEAEs were considered related to trial product.

4202-HVS-102
A total of 15 TEAEs were reported in 9 (34.6%) participants. The most common TEAE reported was headache; 5 events in 4 (15.4%) participants. All TEAEs were non-serious, 14 were Grade 1 in severity and 1 (toothache) was considered Grade 2. Eight (8) TEAEs in 5 (19.2%) participants were reported as possibly related to the trial product. All TEAEs resolved without treatment. No participants had dose reductions, dose interruptions, or discontinued trial product due to TEAEs.

4202-HVS-103
A total of 2 TEAEs were reported in 1 (16.7%) participant; 1 TEAE was upper abdominal pain and 1 was nausea. All TEAEs were non-serious, Grade 1 and resolved with no sequelae. The single event of nausea was reported as possibly related to trial product. There were no dose reductions, dose interruptions or discontinuations in trial product due to TEAEs in this study.

4202-HVS-104
In Part 1, a total of 20 TEAEs were reported in 6 (37.5%) participants, including 3 headache events reported by 2 (12.5%) participants and 2 events of abdominal distension, lower abdominal pain, diarrhoea and nausea, each reported by 2 (12.5%) participants. Remaining events were reported by 1 (6.3%) participant each. All TEAEs were non-serious, 16 were Grade 1 in severity and 4 were Grade 2. Two (2) TEAEs (headache) were reported in 2 (12.5%) participants as possibly related to the trial product (etavopivat and/or itraconazole).
In Part 2, a total of 46 TEAEs were reported in 12 (75.0%) participants with most events reported following phenytoin administration alone. The most common TEAEs reported were headache (6 events in 4 participants), insomnia (3 events in 3 participants), constipation (5 events in 5 participants) and abdominal distension, upper respiratory tract infection, rash and pruritus (2 events in 2 participants each). Remaining events were each reported by 1 (6.3%) participant. All TEAEs were non-serious, most were Grade 1 or 2, and 3 were considered as possibly related to trial product (etavopivat and/or phenytoin). The trial product was withdrawn from 1 participant in Part 2 due to Grade 3 laboratory TEAEs of decreased counts for lymphocytes, neutrophils and white blood cells. However, this event was not considered related to the study product. A single scheduled dose of phenytoin was halted for 1 participant due to TEAEs (Grade 1 rash and Grade 2 pruritus). This was not considered related to the study product.

4202-HVS-105
A total of 110 TEAEs were reported in 38 (59.4%) participants across both study parts. The most common TEAEs reported were headache (16 events in 13 [20.3%] participants), constipation (13 events in 13 [20.3%] participants) and nausea (5 events in 5 [7.8%] participants), back pain (3 events in 3 [4.7%] participants), diarrhoea (3 events in 3 [4.7%] participants) and erythema (3 events in 3 [4.7%]

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participants). TEAE frequency following the first administration of 400 mg etavopivat (2 x 200 mg tablets) was noted to be higher compared to the second administration. A total of 85 TEAEs were considered to be Grade 1 in severity, 23 were Grade 2 and 2 were Grade 3.
Eighty-one (81) TEAEs in 31 (48.4%) participants were reported as possibly related to the trial product, and 4 TEAEs in 3 (4.7%) participants were reported as probably related. Vital sign TEAEs blood pressure (1 event in 1 [1.6%] participant) and heart rate increased (2 events in 2 [3.1%] participants) resolved without sequelae. These were considered possibly related to the trial product. Treatment was withdrawn for 1 participant due to a Grade 1 alanine aminotransferase increase and a Grade 3 aspartate aminotransferase increase. These TEAEs were considered possibly related to the trial product. One (1) participant was withdrawn from treatment due to Grade 1 vomiting (occurring within 2 hours of dosing). One participant experienced increased weight (unrelated to treatment) that remained unresolved at the end of part 1. All TEAEs were resolved at the end of part 2 of the study.

Pooled Treatment Emergent Adverse Events from 4 Studies in Healthy Participants

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	HVS-102	HVS-103	HVS-104		HVS-105	Total
	200 mg	400 mg	Part 1	Part 2	400 mg	
Number of subjects	26	6	16	16	64	128
	N (%) E	N (%) E	N (%) E	N (%) E	N (%) E	N (%) E
All TEAE	9 (34.6) 15	1 (16.7) 2	6 (37.5) 20	12 (75.0) 46	38 (59.4) 110	66 (51.6) 193
TESAE	0	0	0	0	0	0
Adverse events by severity						
Grade 1 (mild)	9 (34.6) 14	1 (16.7) 2	5 (31.3) 16	11 (68.8) 33	34 (53.1) 85	60 (46.9) 150
Grade 2 (moderate)	1 (3.8) 1	0	3 (18.8) 4	6 (37.5) 10	16 (25.0) 23	26 (20.3) 38
Grade 3–5 (severe)	0	0	0	1 (6.3) 3	2 (3.1) 2	3 (2.3) 5
TEAE by relationship						
Probably related	0	0	0	0	3 (4.7) 4	3 (2.3) 4
Possibly related	5 (19.2) 8	1 (16.7) 1	2 (12.5) 2	1 (6.3) 3	31 (48.4) 81	40 (31.3) 95
Unlikely related	2 (7.7) 3	1 (16.7) 1	1 (6.3) 6	3 (18.8) 4	7 (10.9) 11	14 (10.9) 25
Not related	3 (11.5) 4	0	4 (25.0) 12	12 (75.0) 39	7 (10.9) 14	26 (20.3) 69
TEAE leading to						
Dose interruption	0	0	0	0	0	0
Drug withdrawn	0	0	0	1 (6.3) 3	2 (3.1) 3	3 (2.3) 6
Dose reduction	0	0	0	0	0	0
Dose increased	0	0	0	0	0	0

Note: Studies included: 4202-HVS-102, 4202-HVS-103, 4202-HVS-104, 4202-HVS-105. 4202-HVS-104 was a cross-over study, Part 1 evaluated the drug interaction between etavopivat and itraconazole, Part 2 evaluated the drug interaction between etavopivat and phenytoin. The relationship to IMP is based on investigator's assessment.
Abbreviations: BID = twice daily; E = number of events; FE = food effect; IMP = investigational medicinal product; MAD = multiple ascending dose; N = number of participants; % = percentage of participants; QD = once daily; SAD = single ascending dose ; TEAE = treatment emergent adverse events; TESAE = treatment emergent serious adverse events.

In summary, no safety concerns were identified in healthy participants that would prevent further clinical development of etavopivat. The majority of TEAEs were Grade 1 in severity. All TEAEs considered possibly or probably related to the trial product resolved by the end of the study without sequelae.

1.3.2. Safety in Patients with SCD

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The clinical safety evaluation of etavopivat in patients with SCD is based on the results from one completed Phase 1 study (4202-HVS-101) and the Phase 2 dose determination portion of study 4202-HEM-301.

4202-HVS-101

A total of 106 TEAEs were reported in 25 (86.2%) participants with SCD across the SAD, MAD and OLE cohorts in 4202-HVS-101.

SAD Cohort

In the etavopivat 700 mg QD group, 3 TEAEs were reported in 2 (40.0%) participants; 1 (20.0%) participant had a TEAE that required treatment and 1 (20.0%) had a TEAE that was considered possibly related to trial product. In the placebo group, 3 events were reported in 2 (100.0%) participants and 2 participants (100.0%) had TEAEs that required treatment. No TEAEs were considered related to trial product. No TEAE occurred in more than 1 participant in any group. There were single-participant events of arthralgia, palpitations and headache in the etavopivat 700 mg QD group and single-participant events of back pain, myalgia and pruritis in the placebo group. The event of palpitations was considered possibly related to the trial product.

All TEAEs were non-serious and Grade 1 in severity. No participants had dose reductions, dose interruptions or discontinued trial product due to TEAEs.

MAD Cohorts

A total of 30 TEAEs were reported in 13 (81.3%) SCD patients who received etavopivat across both etavopivat MAD cohorts. Events were almost equally distributed across the two cohorts (14 events in the etavopivat 300 mg QD group; 16 events in the etavopivat 600 mg QD group).

The most common TEAEs reported were sickle cell anaemia with crisis (4 events in 3 [37.5%] participants in etavopivat 300 mg QD and 3 events in 3 [37.5%] participants in 600 mg QD groups), headache (3 events in 3 [37.5%] participants in the etavopivat 300 mg QD group and 1 event in 1 [12.5%] participant in the etavopivat 600 mg QD group) and nausea (2 events in 2 [25.0%] participants in the etavopivat 300 mg QD group).

A total of 3 TEAEs in 3 (18.8%) participants in the MAD cohorts were considered possibly related to trial product (2 events in 2 [25%] participants in the etavopivat 300 mg QD group and 1 event in 1 [12.5%] participant in the etavopivat 600 mg QD group). All TEAEs were Grade 1 or 2, with the exception of 1 event in 1 participant in the etavopivat 600 mg QD group and 2 events in 1 participant in the placebo group. One (1) (25.0%) participant in the placebo group had a Grade 3 TEAE of blood creatine phosphokinase increased and a Grade 4 (life-threatening consequences) TEAE of blood creatine phosphokinase increased. One (1) (12.5%) participant in the etavopivat 600 mg QD group had a Grade 3 TESAE of sickle cell anaemia with crisis. No participants had dose reductions, dose interruptions or discontinued the trial product due to TEAEs. No participants died due to TEAEs.

Open-Label Cohort

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- A total of 63 TEAEs were reported in 15 (100%) participants. The most common TEAEs reported were sickle cell anaemia with crisis (11 events in 7 [46.7%] participants), headache (6 events in 4 [26.7%] participants), upper respiratory tract infection (3 events in 3 [20.0%] participants), nausea (3 events in 3 [20.0%] participants) as well as dizziness, migraine, musculoskeletal chest pain, non-cardiac chest pain and increased gamma-glutamyl transferase (2 events in 2 [13.3%] participants each).
- Sixteen (16) TEAEs in 7 (46.7%) participants were considered possibly related to the trial product, and 7 TEAEs in 4 (26.7%) participants were considered probably related. These included sickle cell anaemia with crisis (3 events in 3 [20.0%] participants), headache (4 events in 2 [13.3%] participants), and increased gamma-glutamyl transferase (2 events in 2 [13.3%] participants). Most TEAEs were non-serious, Grade 1 or 2 in severity. Grade 3 TEAEs included 3 events of sickle cell anaemia with crisis in 2 (13.3%) participants and single-participant events of acute chest syndrome (ACS), blood creatine phosphokinase abnormal, coronavirus infection, deep vein thrombosis (DVT), musculoskeletal chest pain, non-cardiac chest pain, pain in extremity and syncope. One (1) Grade 4 (life-threatening consequences) TEAE of blood creatinine phosphokinase abnormal was reported in 1 participant. There were no Grade 5 events.
- Eight (8) TESAEs were reported in 5 (33.3%) participants. There were 4 off-treatment events in 3 (20.0%) participants (ACS and sickle cell anaemia with crisis in 1 participant, non-cardiac chest pain in 1 participant and syncope in 1 participant) and 3 on-treatment events in 2 (13.3%) participants (coronavirus infection and sickle cell anaemia with crisis in 1 participant and DVT in 1 participant).
- All TESAEs were Grade 3 and considered unrelated to the trial product, except the DVT, which was considered as possibly related. One (1) (6.7%) participant reported a TESAE (DVT, Grade 3, possibly related) that led to study discontinuation. There were 2 (13.3%) patients who experienced TEAEs that resulted in dose interruptions of the trial product.

4202-HEM-301 – Phase 2 Dose Determination Portion

TEAEs were reported with similar frequency across all treatment groups: 139 events in 17 (81.0%) participants (758.9 events/100 patient years exposure [PYE]) in the etavopivat 200 mg group, 124 events in 18 (90.0%) participants (741.1 events/100 PYE) in the etavopivat 400 mg group, and 135 events in 18 (94.7%) participants (811.4 events/100 PYE) in the placebo group.

In all treatment groups, the majority of TEAEs were non-serious, Grade 1 (mild) or 2 (moderate) in severity, not related or unlikely related to study products as judged by the investigator and recovered or resolved with no action taken to the study drug. No TEAEs with fatal outcome occurred during the reporting period.

All VOC events had to be reported as AEs in the study. Approximately 60% of participants in all treatment groups reported at least one TEAE as a VOC event: 32 events in 11 (52.4%) participants (174.7/100 PYE) in the etavopivat 200 mg group, 25 events in 13 (65.0%) participants (149.4/100 PYE) in the etavopivat 400 mg group, and 39 events in 12 (63.2%) participants (234.4/100 PYE) in the placebo group.

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Summary of Treatment-Emergent Adverse Events - Dose Determination Population

	Placebo (N=19) n (%), # Events	Etavopivat 200 mg (N=21) n (%), # Events	Etavopivat 400 mg (N=20) n (%), # Events	Etavopivat Combined (N=41) n (%), # Events
TEAEs	18 (94.7), 135	17 (81.0), 139	18 (90.0), 124	35 (85.4), 263
TEAEs Reported as VOC	12 (63.2), 39	11 (52.4), 32	13 (65.0), 25	24 (58.5), 57
Drug-Related TEAEs	4 (21.1), 4	9 (42.9), 19	7 (35.0), 19	16 (39.0), 38
TEAEs Grade ≥3	8 (42.1), 11	9 (42.9), 28	8 (40.0), 16	17 (41.5), 44
Drug-Related TEAEs Grade ≥3	0	2 (9.5), 3	3 (15.0), 3	5 (12.2), 6
Serious TEAEs	3 (15.8), 3	5 (23.8), 5	4 (20.0), 5	9 (22.0), 10
Serious Drug-Related TEAE	0	1 (4.8), 1	1 (5.0), 1	2 (4.9), 2
TEAEs leading to				
Study Drug Discontinuation	0	2 (9.5), 2	0	2 (4.9), 2
Deaths	0	0	0	0
Dose Reduction	0	4 (19.0), 8	4 (20.0), 8	8 (19.5), 16
Dose Interruption	4 (21.1), 4	4 (19.0), 7	2 (10.0), 2	6 (14.6), 9

Note: A TEAE is defined as an adverse event that started or worsened after the first dose of study drug through 28 days after the last dose. Only TEAEs during the double-blind treatment period (or within 28 days of discontinuation) are included.
Severity of adverse event was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5 grading scale (Grades 1–5).
Related TEAEs are TEAEs that were considered possibly related or related to study drug or TEAEs with missing relationship.
Abbreviations: n = number of participants with an event; N = number of participants per cohort; TEAE = treatment-emergent adverse event; VOC = vaso-occlusive crisis.

Overall, the most common TEAE by PT was sickle cell anaemia with crisis, 18 events in 8 (38.1%) participants in the etavopivat 200 mg, 32 events in 14 (70.0%) participants in the etavopivat 400 mg, and 48 events in 14 (73.7%) participants in the placebo group. For participants receiving etavopivat (both dose groups combined), the other most frequently (≥10% of participants) reported TEAEs (by PTs) were: back pain (11 events in 7 [17.1%] participants), pain in extremity (9 events in 7 [17.1%] participants), arthralgia (10 events in 6 [14.6%] participants), A greater number of TEAEs were judged by the investigator as possibly or probably related to the study drug in the etavopivat groups than in the placebo group: 19 events in 9 (42.9%) participants (103.7 events/100 PYE) in the etavopivat 200 mg group, 19

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events in 7 (35.0%) participants (113.6 events/100 PYE) in the etavopivat 400 mg group, and 4 events in 4 (21.1%) participants (24.0 events/100 PYE) in the placebo group. Two possibly or probably study drug-related events were reported as SAEs.

A total of 5 SAEs were reported for 5 (23.8%) participants (27.3 events/100 PYE) in the etavopivat 200 mg group and 4 (20.0%) participants (29.9 events/100 PYE) in the etavopivat 400 mg group, while 3 SAEs were reported for 3 (15.8%) participants (18.0 events/100 PYE) in the placebo group. Most SAEs were reported for a single participant each; the only serious TEAE reported for > 1 participant receiving etavopivat was PT coronavirus disease 2019 (COVID-19) infection (2 [4.9%] participants). There was no apparent relationship between daily etavopivat exposure and incidence of SAEs. All the SAEs required additional treatment, except for PT hepatic enzyme increased, and all the events were resolved. Overall, 2 SAEs were reported by the investigator to be possibly/probably related to the study drug in the etavopivat groups (etavopivat 200 mg PT hepatic enzyme increased; etavopivat 400 mg PT Hb decreased). Two (2) SAEs (PTs hepatic enzyme increased and cerebrovascular accident) leading to permanent discontinuation of the study drug were reported for 2 (9.5%) participants; both in the etavopivat 200 mg group.

In adult and adolescent patients with SCD, the incidence of TEAEs for etavopivat (200 mg or 400 mg) was comparable to placebo. The majority of reported TEAEs were non-serious, mild in severity, and considered unrelated to the study drug by the investigator.

Other Safety Issues

For the SCD cohorts (4202-HVS-101) there were no adverse, clinically meaningful changes in vital signs or physical examination findings. There were no adverse shifts in chemistry, liver function or haematology laboratory parameters.

For the healthy subject cohorts in all completed Phase 1 studies, analysis of vital sign assessments and laboratory tests did not reveal any notable pattern of change following trial product administration.

For the Phase 2 dose determination portion of 4202-HEM-301, analysis of vital sign assessments and laboratory tests did not reveal any notable pattern of change following administration of etavopivat 200 mg or 400 mg compared to placebo. Haematology laboratory parameters were as expected for patients with SCD and did not show an imbalance among the treatment groups.

Electrocardiogram

In study 4202-HVS-101, there were no clinically significant abnormal 12-lead ECG findings across all healthy participant cohorts, nor in SAD and MAD cohorts with SCD. In the OLE cohort, there was 1 clinically significant abnormal 12-lead ECG finding in the etavopivat 400 mg QD group.

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In the 4202-HVS-101 SAD cohort, 1 asymptomatic TEAE of ventricular arrhythmia (Grade 1, considered possibly related to trial product) was reported in 1 healthy participant who received 400 mg of etavopivat; the event resolved without treatment.
In the Phase 2 dose determination portion of 4202-HEM-301, there were 2 (9.5%) ECG results classified as abnormal clinically significant in the etavopivat 200 mg group, and no such results in the etavopivat 400 mg and placebo groups.

Chemistry Laboratory

In the Phase 2 dose determination portion of 4202-HEM-301, chemistry laboratory parameters indicated a worsening to Grade 3 from baseline in the etavopivat 400 mg group (creatinine increased, and hypoglycaemia; 1 [5.0%] participant for each); and in the placebo group (hyperkalaemia, hypocalcaemia, and hypomagnesaemia; 1 [5.3%] participant for each). In all treatment groups, no chemistry laboratory parameters worsened to Grade 4 from baseline. The shifts in chemistry laboratory parameters were assessed as SCD-related and did not show an imbalance between the treatment groups.

Liver Function

In the Phase 2 dose determination portion of the 4202-HEM-301 study, evaluation of laboratory results showed increased liver enzymes worsening to Grade 3 from the baseline in 3 participants in etavopivat groups, etavopivat 200 mg (alanine aminotransferase increased; 2 [9.5%] participants, aspartate aminotransferase increased; 1 [4.8%] participant) and etavopivat 400 mg (gamma-glutamyl transferase increased; 1 [5.0%] participant). The impairments in liver enzymes were considered possibly study drug-related by the investigator, but clear alternative aetiologies were found in all participants except one.

QT Prolongation Risk Assessment

Based on ICH E14 (R3),63 concentration-QT modelling is a reasonable substitute for a dedicated Thorough-QT (TQT) study to classify the risk of QTc prolongation. Therefore, all healthy subject SAD cohorts included collection of high-quality ECG data (continuous monitoring obtained using telemetry or 12-lead Holter read centrally) to support an evaluation of the relationship between etavopivat plasma concentration and the potential effects on the QT interval.
No QTc prolongation effect was observed for etavopivat at all dose levels tested. Mean (90% CI) for the model-predicted placebo-adjusted change from baseline in QTcF interval at the 1000 mg dose level was -1.06 (-5.91, 3.79) ms.

Clinical Efficacy and Safety Assessment

- The clinical development programme for etavopivat has been conducted in accordance with applicable regulatory and GCP requirements and is considered adequate to support progression to Phase 3 clinical

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development. The completed clinical studies appropriately address clinical pharmacology, safety, and preliminary efficacy in healthy participants and in patients with sickle cell disease (SCD). The overall clinical strategy, including the conduct of SAD, MAD, food-effect, formulation-bridging, mass balance, and drug–drug interaction studies, is consistent with regulatory expectations for a product intended for chronic administration.

- The Phase 2 dose determination portion of study 4202-HEM-301 was randomised, placebo-controlled, double-blind, and multicentre, which is considered appropriate for dose selection and exploratory assessment of efficacy and safety. The study was not powered to demonstrate efficacy, and therefore conclusions regarding clinical benefit are limited. The selected efficacy endpoints (haemoglobin response, vaso-occlusive crisis [VOC] outcomes, markers of haemolysis, and quality-of-life measures) are aligned with current regulatory expectations for clinical development in SCD.

Overall, the submitted clinical data are considered sufficient to support continuation into Phase 3, acknowledging that confirmatory evidence of efficacy and a comprehensive characterisation of long-term safety are pending.

Pharmacokinetics, Metabolism, and Drug–Drug Interactions

- Following oral administration, etavopivat was rapidly absorbed, with approximately dose-proportional increases in systemic exposure across the investigated dose range. The pharmacokinetic profile was broadly comparable between healthy participants and patients with SCD. Human mass balance and metabolite profiling studies demonstrated extensive metabolism, with the glucuronide metabolite M633/1 representing the major circulating drug-related component. The primary route of elimination was via the faeces, with urinary excretion constituting a minor pathway.
- Food did not have a clinically relevant impact on overall exposure for the tablet formulation. Administration of the granule formulation with soft food increased peak exposure without affecting total exposure. While pharmacokinetic similarity between tablet and granule formulations was demonstrated, formal bioequivalence was not established, which may require consideration in the context of paediatric use.
- Drug–drug interaction studies showed that co-administration with a strong CYP3A4/P-gp inhibitor resulted in a moderate increase in exposure that remained within previously tolerated ranges. In contrast, co-administration with a strong CYP3A4/P-gp inducer substantially reduced etavopivat exposure. The proposed restriction of strong inducers is considered appropriate from a regulatory perspective.

Pharmacodynamics and Mechanism of Action

- Etavopivat demonstrated consistent pharmacodynamic effects in both healthy participants and patients with SCD, characterised by reductions in 2,3-diphosphoglycerate, increases in adenosine triphosphate, and increased haemoglobin–oxygen affinity. These effects were observed rapidly after dosing and were

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sustained with repeated administration. Pharmacokinetic/pharmacodynamic modelling suggested a plateau in pharmacodynamic response at doses ≥400 mg once daily, supporting the selected dose range for further clinical evaluation.

- In patients with SCD, pharmacodynamic changes were accompanied by improvements in red blood cell functional parameters, including measures of deformability, haemoglobin polymerisation, oxidative stress, and membrane integrity. These findings support target engagement and are considered consistent with the proposed mechanism of action.

Efficacy

- Efficacy data for etavopivat are currently limited to patients with SCD. No clinical efficacy data are available to date in patients with thalassaemia or myelodysplastic syndrome, and efficacy in these indications remains to be established.
- Short-term and open-label studies in patients with SCD demonstrated increases in haemoglobin levels and improvements in markers of haemolysis. These effects were generally observed within the first weeks of treatment and were sustained during continued dosing, with gradual return towards baseline following treatment discontinuation.
- In the Phase 2 dose determination portion of study 4202-HEM-301, numerically favourable trends were observed for key efficacy endpoints, including haemoglobin response rates, annualised VOC rates, and time to first VOC, in both etavopivat dose groups compared with placebo. However, the study was not powered for formal statistical comparisons, and the observed treatment effects were variable, with overlapping confidence intervals for several endpoints. Consequently, the clinical relevance and consistency of these findings require confirmation in the ongoing Phase 3 portion of the study.

Safety

- The safety profile of etavopivat has been evaluated in multiple Phase 1 studies in healthy participants and in patients with SCD, as well as in the Phase 2 dose determination study. Across studies, etavopivat was generally well tolerated.
- In healthy participants, the majority of treatment-emergent adverse events (TEAEs) were mild or moderate in severity and resolved without sequelae. No consistent dose-related safety signals were identified. Isolated findings, including transient laboratory abnormalities and an asymptomatic ventricular arrhythmia, were not associated with clinically significant outcomes.
- In patients with SCD, the overall incidence and nature of TEAEs were consistent with the underlying disease and were broadly comparable between etavopivat and placebo in the Phase 2 study. Vaso-occlusive events were frequently reported as TEAEs across all treatment groups, as expected in this population. Serious adverse events occurred at similar rates across groups, with no clear exposure–response relationship. A limited number of serious adverse events were considered possibly related to

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etavopivat, including hepatic enzyme elevations and a thromboembolic event, which warrant continued monitoring.

- Laboratory assessments, vital signs, and electrocardiographic evaluations did not reveal consistent or clinically relevant safety concerns. Increases in liver enzymes were observed in a small number of participants and were generally associated with alternative aetiologies; however, a causal relationship to etavopivat cannot be fully excluded. Concentration–QT modelling did not indicate a clinically relevant risk of QT prolongation, and the absence of a dedicated thorough QT study is considered acceptable in line with ICH E14(R3).

Overall Clinical Assessment

Based on the submitted data, the clinical pharmacology, safety, and preliminary efficacy profile of etavopivat is considered adequate to support Phase 3 clinical development in patients with SCD. The available data demonstrate target engagement and pharmacodynamic activity consistent with the proposed mechanism of action. While preliminary efficacy signals have been observed, definitive conclusions regarding clinical benefit await confirmation from adequately powered Phase 3 studies. No safety findings have been identified to date that would preclude continued clinical development, subject to ongoing monitoring of hepatic and thromboembolic events.

- **Protocol:** An Open-Label, Multi-Centre, Rollover Study to Characterise Long-Term Safety and Efficacy of Etavopivat in Adults, Adolescents and Children who Have Sickle Cell Disease or Thalassemia and have Completed a Treatment Period in an Etavopivat Study (FLORAL)
- **Phase:** 3b
- **Objective(s):**

Study Objectives and Endpoints

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Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
To investigate long-term safety of etavopivat in adults, adolescents and children with SCD, SCD_{TD}, TDT or NTDT transferring from other studies with etavopivat	*Primary*		
	Number of TEAEs, reported for each indication and age group separately	Baseline (week 0 of FLORAL) to end of study (week 264, or earlier[a])	Count
	Number of adverse reactions, reported for each indication and age group separately	Baseline (week 0 of FLORAL) to end of study (week 264, or earlier[a])	Count
Secondary	Title	Time frame	Unit
To investigate long-term clinical efficacy measures of etavopivat treatment in adults, adolescents and children with SCD transferring from other studies with etavopivat[b]	*Supportive*		
	Annualised VOC rates, reported for each age group separately	Baseline (week 0 of FLORAL) to end of treatment at week 260, or earlier[c]	Count
	Change in VOCs, reported for each age group separately	Baseline (of parent study[d]) to end of treatment at week 260, or earlier[c]	Count
	Change in Hb concentration, reported for each age group separately	Baseline (of parent study[d]) to end of treatment at week 260, or earlier[c]	g/dL
To evaluate the effects of etavopivat on hospitalisations in adults, adolescents and children with SCD transferring from other studies with etavopivat[b]	Annualised number of hospitalisations, reported for each age group separately	Baseline (week 0 of FLORAL) to end of treatment at week 260, or earlier[c]	Count
	Average length of stay of hospitalisations, reported for each age group separately	Baseline (week 0 of FLORAL) to end of treatment at week 260, or earlier[c]	Days
To investigate long-term clinical efficacy measures of etavopivat treatment in adults and adolescents with NTDT transferring from other studies with etavopivat	Change in Hb concentration	Baseline (of parent study[d]) to end of treatment at week 260, or earlier[c]	g/dL

[a] This study is expected to end in November 2029, after 264 weeks, or when etavopivat is commercially available in the respective participating countries, whichever comes first.

[b] Not including participants with SCDTD.

[c] The treatment period may end earlier depending on when etavopivat is commercially available in the respective participating countries.

[d] Baseline of the parent study (i.e., the previous etavopivat study that a participant is rolling over from) is defined as the last 1 (or 2, if applicable) measurement before study treatment was given.

Note: Participants will be grouped into cohorts according to age: adults and adolescents (i.e., participants ≥ 12 years old) and children, (i.e., participants ≥ 11 months to < 12 years old); and indication (SCD, SCD_{TD}, NTDT, or TDT) Note: Participants with SCD_{TD} or TDT were defined as chronically transfused in the parent studies, i.e., with receipt of ≥ 6 RBC units in the previous 24 weeks before the first dose of study treatment, and no transfusion-free period for > 35 days during that period.

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Abbreviations: Hb = hemoglobin; LDH = lactate dehydrogenase; NTDT = non-transfusion-dependent thalassemia; RBC = red blood cell; SAE = serious adverse event; SCD = sickle cell disease; SCD_{TD} = participants with SCD on chronic RBC transfusions; TDT = transfusion-dependent thalassemia; TEAE = treatment-emergent adverse event; VOC = vaso-occlusive crisis.

- **Rationale:**

The purpose of this rollover study is to investigate the long-term safety of etavopivat in participants 11 months of age and older (12 years and older in Egypt, since the two parent studies conducted in Egypt "4202-HEM-201 and 4202-HEM-301" did not include children less than 12 years old) with SCD or thalassemia who have completed a treatment period in previous etavopivat studies (parent studies). Long-term clinical efficacy measures of etavopivat treatment will also be assessed. This study is to ensure that participants who are benefiting from etavopivat treatment have prolonged access to the drug in the time before it is commercially available in their country.

The study population will include participants with SCD who are not on chronic transfusions, participants with SCD who have been on chronic transfusions to prevent primary stroke or recurrence of stroke (SCD_{TD}), participants with non-transfusion dependent thalassemia (NTDT), and participants with transfusion-dependent thalassemia (TDT). For participants with TDT or SCD_{TD}, who were defined as chronically transfused in their parent studies, chronic transfusion was defined as receipt of $\geq$ 6 RBC units in the previous 24 weeks before the first dose of study treatment, and no transfusion-free period for > 35 days during that period.

In patients with SCD, treatment with etavopivat is anticipated to reduce the rate of sickle cell polymerization and improve RBC membrane function, thereby reducing RBC sickling and RBC hemolysis that led to vascular obstruction and anemia, two hallmarks of SCD pathology.

In patients with SCD on chronic transfusion to prevent primary stroke or recurrence of stroke treatment with etavopivat is also anticipated to reduce the need for RBC transfusions through improving the health and lifespan of SCD RBCs, and the lifespan of transfused healthy RBCs.

In patients with NTDT, treatment with etavopivat is anticipated to improve the ability of erythrocyte precursors and mature RBCs to manage metabolic and oxidative stress caused by aggregation of mismatched globin chains. These improvements are expected to result in more effective erythropoiesis, decreased hemolysis and increased RBC lifespan, leading to increased Hb levels.

In patients with TDT, treatment with etavopivat is expected to likewise increase the lifespan of the transfused, healthy RBCs. Combined, the effects on erythropoiesis, on mature thalassemia RBCs and on transfused RBCs are expected to reduce the need for transfusions.

Scientific Rationale for Study Design

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The study population will include children, adolescent and adult participants with SCD and adolescents and adults with SCD_{TD}, NTDT or TDT who have completed a treatment period previously in an etavopivat study. An open label design is considered the most suitable to investigate long-term safety. To ensure that participants benefitting from etavopivat can remain on treatment, the participants are planned to have visit 1 (V1) of this study combined with the end of treatment (EOT) visit in the respective parent study.

The key design elements of the study are the same for the disease indications within the study population, including the primary endpoint, inclusion and exclusion criteria, most assessments, study duration, and visit structure.

This study will increase the knowledge of the safety profile of etavopivat as well as generating long-term safety data. This open-label study has a treatment duration of up to 260 weeks to provide access to etavopivat for all participants for an extended period. This is a non-comparative study, therefore there will be no formal treatment comparison, and all endpoints will be summarized descriptively.

Parent Studies

Parent study ID	Phase	Participant Age	Indications(s)
Hibiscus (4202-HEM-301)	2/3	12 to 65 years	SCD
Gladiolus (4202-HEM-201)	2	12 to 65 years	SCD_{TD}, NTDT and TDT
Hibiscus Kids (4202-HEM-202)	1/2	6 months to < 18 years	SCD
4202-HEM-204	2	12 to 16 years	SCD with increased risk of primary stroke

- **Design:**

This is an interventional, multi-national, multi-centre, open-label, phase 3b study. The study primarily aims to assess long-term safety, and secondarily long-term efficacy, in enrolled adults (participants ≥ 18 years old), adolescents (participants ≥ 12 to < 18 years old) and children (participants ≥ 11 months to < 12 years old) with SCD, SCD_{TD}, NTDT or TDT. Approximately 325 participants are planned to be enrolled in the study.

Only participants who have completed a treatment period of an etavopivat study and had clinical benefit from etavopivat treatment (as determined by the investigator) without permanent discontinuation of study intervention are eligible for this open-label study. All participants ≥ 12 years old will receive etavopivat tablets orally, of 400 mg dose. Participants < 12 years of age will receive etavopivat mini tablets orally in age- and weight-adjusted doses.

The study consists of:

- A transfer visit (V1) where participants transfer to FLORAL from their previous etavopivat study (parent study).

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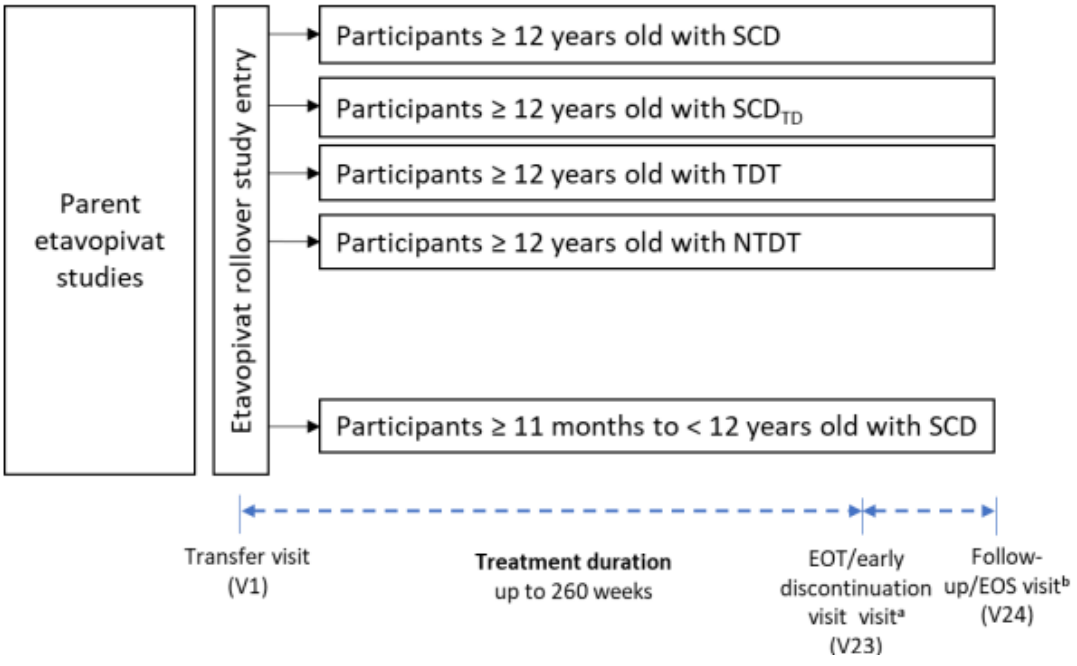
- Up to 260 weeks of intervention period in which participants will receive etavopivat.
- A 4-week follow-up period, with a safety follow-up/end of study (EOS) visit (V24) taking place 4 weeks after the last etavopivat dose or starting tapering of etavopivat.

Treatment duration with etavopivat in this study will be for up to 260 weeks in total. This study is expected to end in November 2029 or when etavopivat is commercially available in the respective participating countries, whichever comes first (The sponsor is committed to provide etavopivat to participants in Egypt until being commercially available even if FLORAL study ended before.) Because participants will enroll from the parent studies at different timepoints, the treatment duration for individual participants in this study will be different. Participants with the longest duration in this study will receive treatment for up to 260 weeks (from V1 to V23). If etavopivat becomes commercially available, participants in the applicable countries will enter the EOT/early discontinuation visit (V23), independent of the visit number. Moreover, a follow-up/EOS visit (V24) will be performed for all participants 4 weeks following the EOT/early discontinuation visit (V23) during this study. Participants switching to commercially available etavopivat will not be required to complete the follow-up/EOS visit (V24).

Study Design



Abbreviations: EOT = end of treatment; EOS = end of study; RBC = red blood cell; SCD = sickle cell disease; SCDTD = sickle cell disease on chronic RBC transfusions; SoA = schedule of activities; TDT = transfusion-dependent thalassaemia; NTDT = non-transfusion dependent thalassaemia

- **Recommendation &/ or Questions & Answers:**

Screening Requirements (29Dec2024)	Applicant's Reply (Jan 2025)

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	At EDA Application section 5.0.4, a clarification is required about the Planned number of subjects to be included in Egypt (25) since it is less than the number of participants planned to be enrolled in the parent studies ongoing in Egypt which is 95.	The current estimation of how many participants from the parent trials we expect to roll over to the FLORAL study is based on the assumption that 50% of the participants who enroll in the parent trials will eventually proceed to the FLORAL study. This 50% assumption takes into account an anticipated 30% dropout rate in the parent trials. Additionally, we assume that 20% of the remaining participants from the parent trials may either not benefit from the treatment or may not be interested in a long-term commitment to another clinical trial. Therefore, we will update our assumptions in an upcoming protocol amendment to reflect more accurate numbers if needed.
	According to the Executive Regulation 927/2022 of the Clinical Trials Law 214/2020 the sponsor should provide the participants with the IMP even the trial is ended before the market authorization of the drug in Egypt, hence, the post-trial benefit plan is required to be modified accordingly.	We are committed to ensuring compliance with this regulation and will include this provision in the post-trial benefit plan as well as in an upcoming protocol amendment.

- **Abbreviation:**

ACS	Acute Chest Syndrome
AE	Adverse Event
ARC	Absolute Reticulocyte Count
ASCQ-Me	Adult Sickle Cell Quality of Life Measurement Information System
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
AUC0–24	Area Under the Curve from 0 to 24 hours
AUC0–inf	Area Under the Curve extrapolated to infinity
AUC0–t	Area Under the Curve from time zero to last measurable concentration
BCRP	Breast Cancer Resistance Protein
BID	Twice Daily
CA	Central Administration
CI	Confidence Interval
CRC	Clinical Research Center
CT	Clinical Trial
CV%	Coefficient of Variation
CYP	Cytochrome P450

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DD	Dose Determination
DDI	Drug–Drug Interaction
EC50	Half Maximal Effective Concentration
ECG	Electrocardiogram
EDA	Egyptian Drug Authority
EFD	Early Fetal Development
EImax	Maximum Elongation Index
EOS	End of Study
EOT	End of Treatment
FE	Food Effect
GA	General Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratio
Hb	Hemoglobin
Hb-O_2	Hemoglobin–Oxygen
HbSC	Compound Heterozygous Sickle Cell Disease
HbSS	Homozygous Sickle Cell Disease
hERG	Human Ether-à-go-go-Related Gene
HR	Heart Rate
HU	Hydroxyurea
HV	Healthy Volunteers
IB	Investigator's Brochure
IC50	Half Maximal Inhibitory Concentration
IMP	Investigational Medicinal Product
Km	Michaelis–Menten Constant
LDH	Lactate Dehydrogenase
MAD	Multiple Ascending Dose
MATE	Multidrug and Toxin Extrusion
MDCKII	Madin-Darby Canine Kidney II Cells
MDR1	Multidrug Resistance Protein 1
NOAEL	No Observed Adverse Effect Level
NTDT	Non-Transfusion-Dependent Thalassemia
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
OLE	Open Label Extension
PD	Pharmacodynamics
PEP	Phosphoenolpyruvate
P-gp	P-glycoprotein
PI	Principal Investigator

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PK	Pharmacokinetics
PK/PD	Pharmacokinetic / Pharmacodynamic
PoS	Point of Sickling
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
QD	Once Daily
QTcF	QT Interval Corrected (Fridericia)
RBC	Red Blood Cell
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SCD	Sickle Cell Disease
SCDTD	Sickle Cell Disease on Chronic Transfusions
SDD	Spray-Dried Dispersion
SoA	Schedule of Activities
TDT	Transfusion-Dependent Thalassemia
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
tmax	Time to Maximum Concentration
UGT	Uridine Diphosphate Glucuronosyltransferase
VOC	Vaso-Occlusive Crisis
WT	Wild Type

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