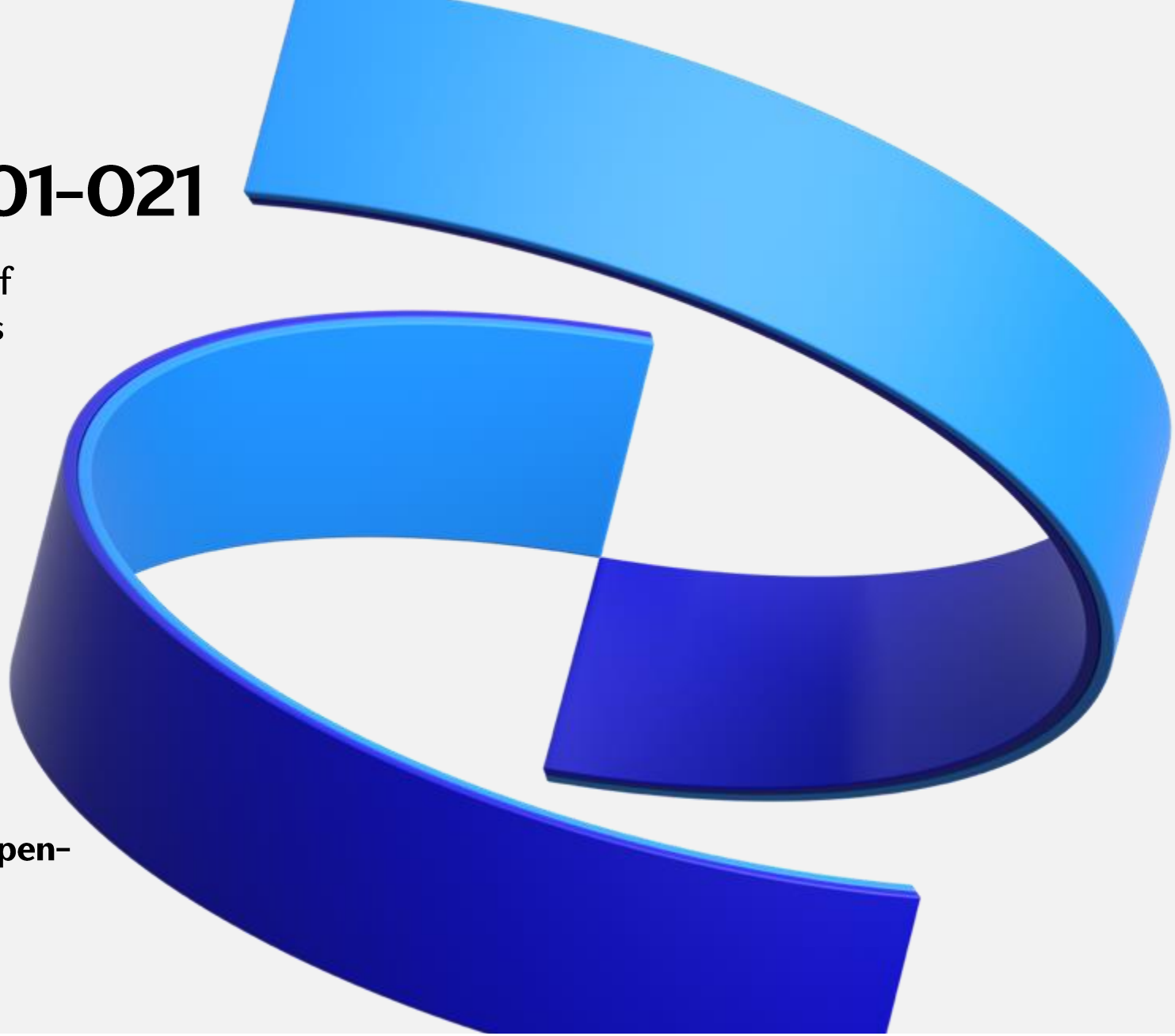
C5351004 / GBT021601-021

A Phase 2/3 Randomized, Multicenter Study of Osivelotor Administered Orally to Participants With Sickle Cell Disease

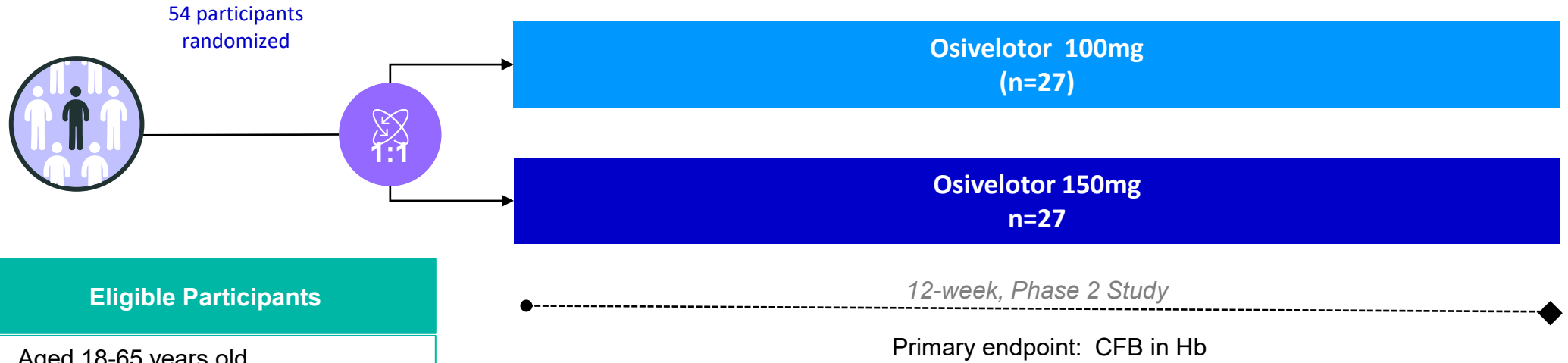
NCT05431088



Final results from Part A: Phase 2 randomized, open-label, 12-week, dose-finding study

C5351004 / GBT021601-021 : Phase 2/3 Study in Participants With Sickle Cell Disease

The phase 2 study was a randomized (1:1), open-label, 12-week, dose-finding study



Eligible Participants

- Aged 18-65 years old
- SCD with HbSS or HbSβ^0 genotype
- Hb 5.5-10.5g/dL
- ≤10 VOCs reported within the 12 months prior to screening

Eligible participants completing Week 12 of the phase 2 study could enter the OLE study

CFB, change from baseline; Hb, hemoglobin; HbSS, homozygous hemoglobin S genotype; HbSβ^0, heterozygous hemoglobin S/β^0-thalassemia genotype; SCD,sickle cell disease; VOC,vaso-occlusive crisis

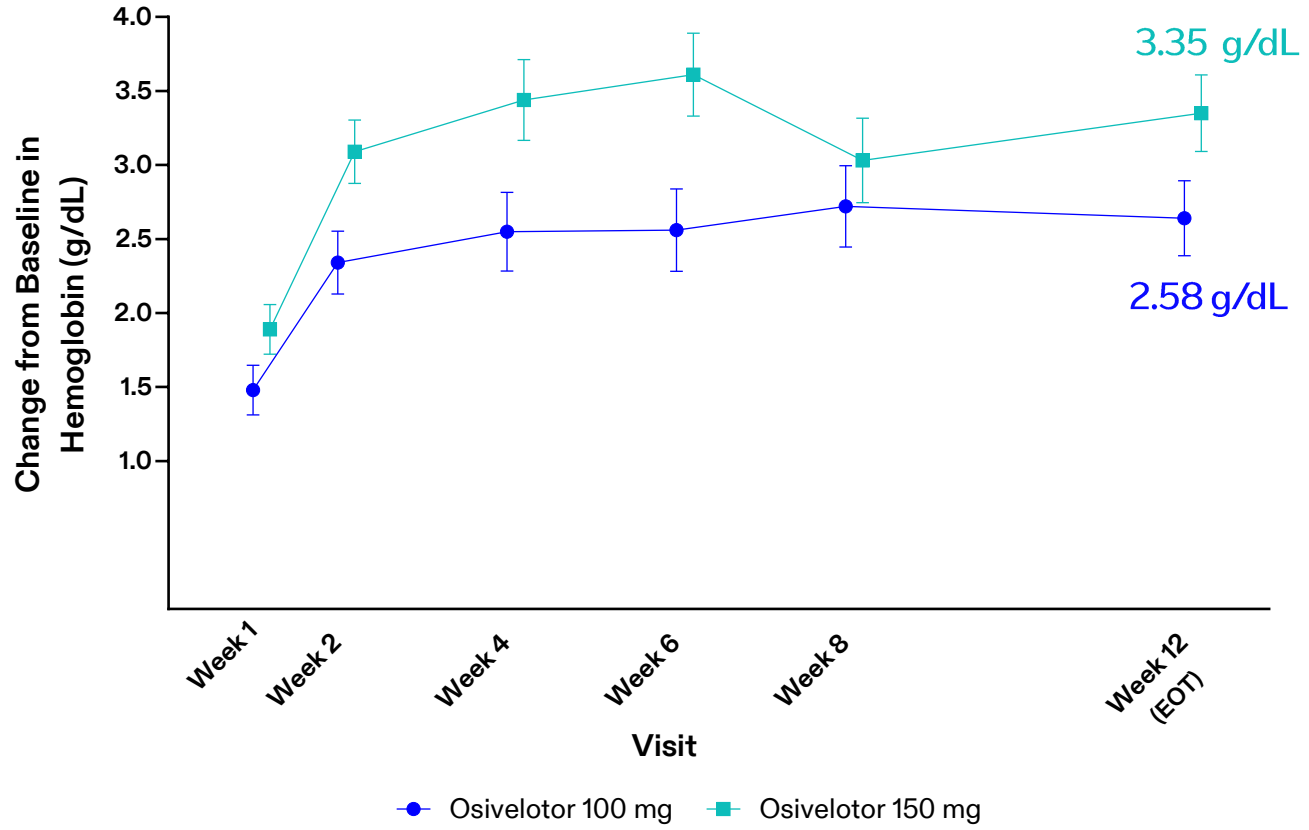
Phase 2 study, NCT05431088; open-label extension, NCT05632354

Participant Baseline Characteristics

Parameter	Osivelotor 100 mg (N=27)	Osivelotor 150 mg (N=27)	Osivelotor 100 mg + 150 mg (N=54)
Age (years)			
Mean (SD)	28.4 (10.57)	28.2 (11.54)	28.3 (10.96)
Median	23.0	24.0	23.5
Min, Max	18, 53	18, 59	18, 59
Sex, n (%)			
Female	14 (51.9%)	16 (59.3%)	30 (55.6%)
Geographic Region, n (%)			
North America	6 (22.2%)	6 (22.2%)	12 (22.2%)
Sub-Saharan Africa (Nigeria)	21 (77.8%)	21 (77.8%)	42 (77.8%)
SCD genotype, n (%)			
HbSS	26 (96.3%)	26 (96.3%)	52 (96.3%)
HbSβ0	1 (3.7%)	1 (3.7%)	2 (3.7%)
HU use at screening, n (%)			
Yes	8 (29.6%)	12 (44.4%)	20 (37.0%)
Annualized incidence rate of VOC 12 months prior	1.67	2.19	1.93
Baseline Hemoglobin, mean (SD) g/dL	8.43 (1.006)	8.47 (1.237)	

HU= hydroxyurea; SCD= sickle cell disease; SD= standard deviation; VOC= vaso-occlusive crisis.

Increases in Hemoglobin Were Observed Over the 12-Week Treatment Period

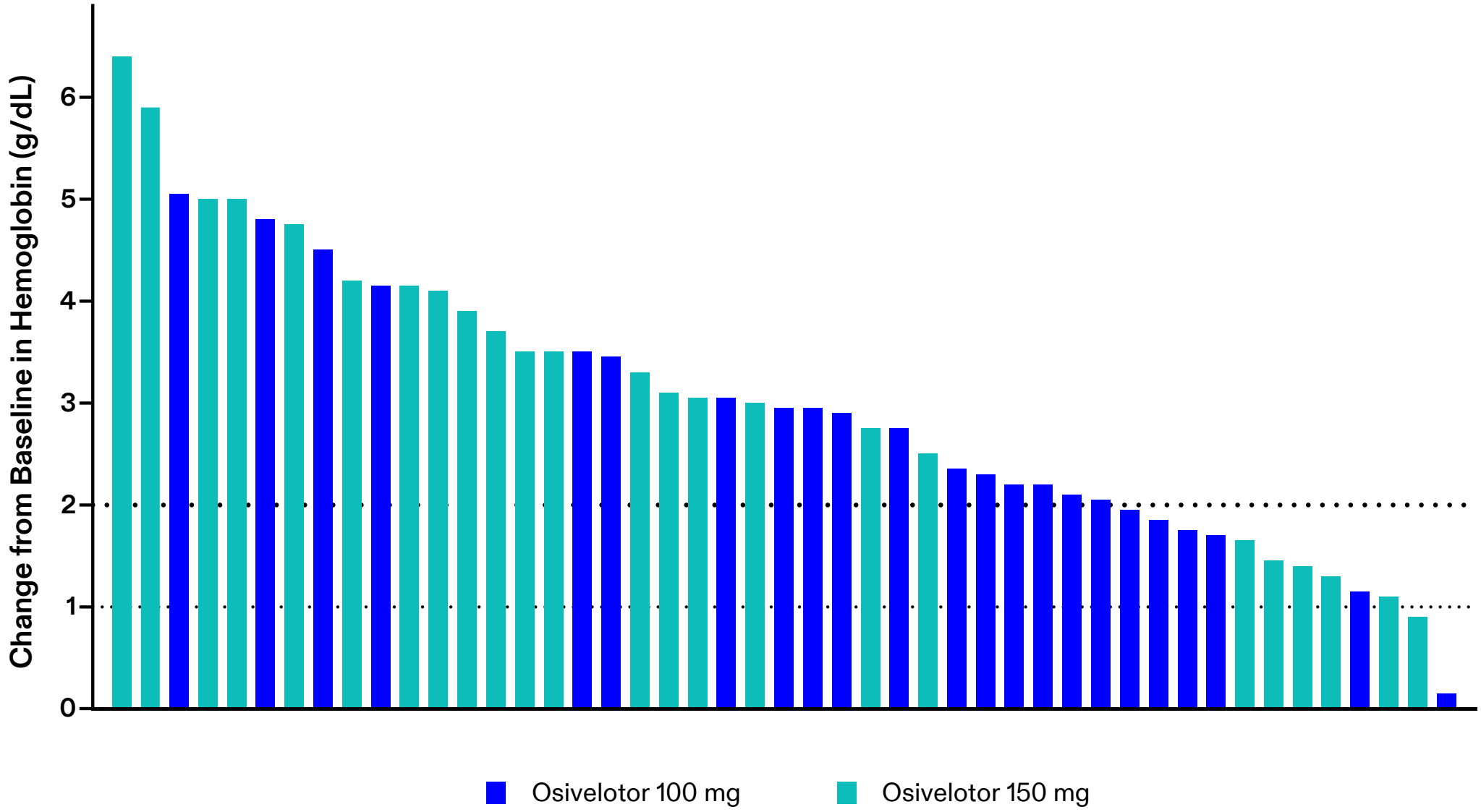


Osivelotor 100 mg	27	25	27	26	25	24
Osivelotor 150 mg	27	25	24	26	23	23

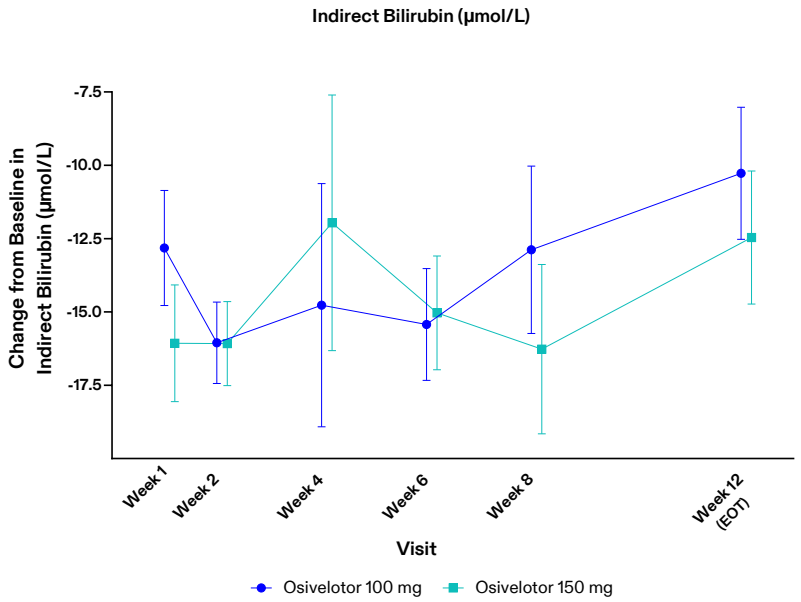
Number of participants

Change from baseline through Week 12 was evaluated with a mixed model for repeated measures adjusted for geographic region, baseline Hb, and baseline HU. The analysis excluded post-randomization measurements obtained on or after initiation of new HU use (for participants with no HU use at baseline), transfusion, or the use of medications known to affect Hb or VOC.
CI=confidence interval; Hb=hemoglobin; HU=hydroxyurea; LS=least squares

The Majority of Participants Achieved Hemoglobin Increases ≥2 g/dL

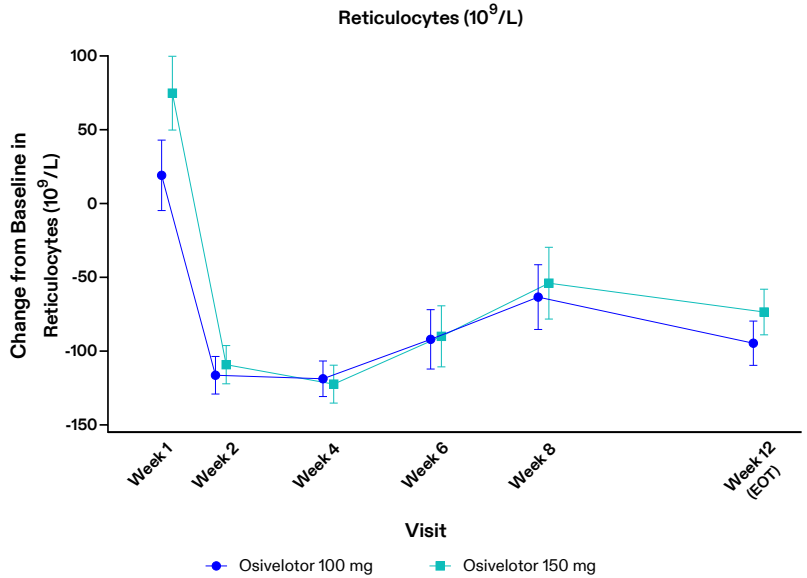


Osivelotor Led to Favorable Reductions in Hemolysis Markers (Indirect Bilirubin, Reticulocytes and Lactate Dehydrogenase)



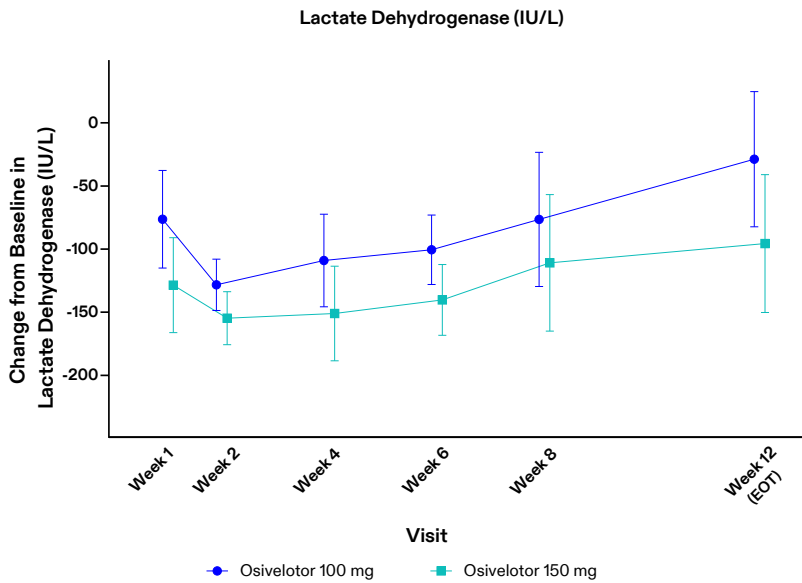
Osivelotor 100 mg	26	25	26	25	25	24
Osivelotor 150 mg	25	23	23	24	24	24

Number of participants



Osivelotor 100 mg	22	20	22	19	20	19
Osivelotor 150 mg	20	19	19	18	16	18

Number of participants



Osivelotor 100 mg	25	27	27	26	25	25
Osivelotor 150 mg	27	25	26	25	24	24

Number of participants

Plots show Least Square Means (Standard Error) for Change from Baseline based on Mixed Model for Repeated Measures (MMRM) Analysis

A Numerically Lower VOC Event Rate Was Observed Over the 12-Week Treatment Period Compared With The Pre-Screening Period

	Pre-Screening (N=54)	On-Treatment (N=54)
Total participant-years	54.0	12.2
Number of VOCs per participant		
0	13(24.1%)	40(74.1%)
1	12(22.2%)	11(20.4%)
2	10(18.5%)	3(5.6%)
3	10(18.5%)	0
4	5(9.3%)	0
5	2(3.7%)	0
6	2(3.7%)	0
Total number of VOCs	104	17
Annualized VOC incidence rate	**1.93**	**1.39**

All but one were uncomplicated VOCs

Annualized VOC rate was calculated using a negative binomial model with participant-years (on-treatment vs prior year) as independent variable, number of VOCs for each participant during corresponding participant-years as response, and natural log of participant-years as offset.
CI=confidence interval; Hb=hemoglobin; HU=hydroxyurea; NSAID=nonsteroidal anti-inflammatory drug; OLE=open-label extension; VOC=vaso-occlusive crisis

The Majority of TEAEs Were Grade 1–2 and Considered Unrelated to Osivelotor

	Osivelotor 100 mg (N=27)	Osivelotor 150 mg (N=27)	Osivelotor 100 mg + 150 mg (N=54)
Number of TEAEs	84	78	162
Participants with at least 1 TEAE, n (%)	**21 (77.8%)**	**21 (77.8%)**	**42 (77.8%)**
Participants by Maximum Severity of TEAEs, n (%):			
Grade 1	7 (25.9%)	5 (18.5%)	12 (22.2%)
Grade 2	6 (22.2%)	14 (51.9%)	20 (37.0%)
Grade 3	6 (22.2%)	1 (3.7%)	7 (13.0%)
Grade 4	1 (3.7%)	0	1 (1.9%)
Grade 5	**1 (3.7%)**	**1 (3.7%)**	**2 (3.7%)**
Number of Treatment-Related TEAEs	13	5	18
Participants with ≥1 Treatment-Related TEAE, n (%)	**5 (18.5%)**	**4 (14.8%)**	**9 (16.7%)**
Maximum Severity of Treatment-Related TEAE, n (%):			
Grade 1	4 (14.8%)	4 (14.8%)	8 (14.8%)
Grade 2	1 (3.7%)	0	1 (1.9%)
Grade 3 - 5	0	0	0

Safety Overview (AEs)

- **100 mg Osivelotor** (N=27): 21 participants reported TEAEs
  - Malaria: 6 participants (22.2%)
  - Headache, Urinary tract infection: 3 participants each (11.1%)
  - Diarrhoea, Pain, Face oedema, Upper respiratory tract infection, Sepsis, Electrocardiogram T wave inversion, Hyperkalaemia, Arthralgia: 2 participants (7.4%)

- **150 mg Osivelotor** (N=27): 21 participants reported TEAEs
  - Malaria: 7 participants (25.9%)
  - Diarrhoea: 5 participants (18.5%)
  - Urinary tract infection, Upper respiratory tract infection, Hyperkalaemia, Arthralgia, Headache: 3 participants (11.1%)
  - Atrioventricular block first degree, Electrocardiogram T wave inversion, Blood creatine phosphokinase increased, Microalbuminuria: 2 participants (7.4%)

Safety Overview (SAEs)

	Osivelotor 100 mg (N=27)	Osivelotor 150 mg (N=27)	Osivelotor 100 mg + 150 mg (N=54)
Number of Treatment-Emergent SAEs	10	3	13
Participants with at least 1 Treatment-Emergent SAE, n (%)	7 (25.9%)	2 (7.4%)	9 (16.7%)
Participants with at least 1 Treatment-Related Treatment-Emergent SAE, n (%)	0	0	0
Participants with TEAE leading to death, n (%)	1 (3.7%)	1 (3.7%)	2 (3.7%)

Two participants from Nigeria experienced fatal events during the study:
- One due to TEAEs of cerebrovascular accident and suspected malaria
- One due to a TEAE of malaria.

Neither fatal event was considered related to Osivelotor.

The Majority of Serious AEs Were Single Occurrences, Each Reported in Only One Participant

System Organ Class Preferred Term	Osivelotor 100 mg (N=27)	Osivelotor 150 mg (N=27)	Osivelotor 100 mg + 150 mg (N=54)
Participants with at least one event	**7 (25.9%)**	**2 (7.4%)**	**9 (16.7%)**
Blood and lymphatic system disorders	**1 (3.7%)**	**0**	**1 (1.9%)**
Haemolysis	1 (3.7%)	0	1 (1.9%)
Gastrointestinal disorders	**1 (3.7%)**	**0**	**1 (1.9%)**
Enteritis	1 (3.7%)	0	1 (1.9%)
General disorders and administration site conditions	**1 (3.7%)**	**0**	**1 (1.9%)**
Face oedema	1 (3.7%)	0	1 (1.9%)
Infections and infestations	**4 (14.8%)**	**1 (3.7%)**	**5 (9.3%)**
Malaria	2 (7.4%)	1 (3.7%)	3 (5.6%)
Osteomyelitis acute	1 (3.7%)	0	1 (1.9%)
Sepsis	1 (3.7%)	0	1 (1.9%)
Urinary tract infection	1 (3.7%)	0	1 (1.9%)
Nervous system disorders	**1 (3.7%)**	**1 (3.7%)**	**2 (3.7%)**
Cerebrovascular accident	0	1 (3.7%)	1 (1.9%)
Seizure	1 (3.7%)	0	1 (1.9%)
Renal and urinary disorders	**0**	**1 (3.7%)**	**1 (1.9%)**
Haematuria	0	1 (3.7%)	1 (1.9%)
Skin and subcutaneous tissue disorders	**1 (3.7%)**	**0**	**1 (1.9%)**
Skin ulcer	1 (3.7%)	0	1 (1.9%)

C5351004 / GBT021601-021 Part A Conclusions

- Hemoglobin change from baseline data suggest that osivelotor has the potential to deliver robust, dose-dependent, and sustained efficacy over the 12-week treatment period.
- Osivelotor led to favorable reductions in hemolysis measures (Indirect Bilirubin, Reticulocytes and Lactate Dehydrogenase)
- Exploratory analyses showed improvements in RBCs deformability at lower oxygen tensions, membrane health, and reduced polymerization.
- A numerically lower VOC event rate was observed during treatment compared with the pre-screening period.
- Osivelotor was generally well tolerated.
- These effects were sustained over the longer term in the open-label extension study C5351005 / GBT021601-022 (NCT05632354).

Collectively, these findings support ongoing clinical development of osivelotor as a potential treatment for individuals with Sickle cell disease.