GBT021601, a Next-Generation HbS Polymerization Inhibitor: Results of Safety, Tolerability, Pharmacokinetics and Pharmacodynamics in Adults Living with Sickle Cell Disease and Healthy Volunteers

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INTRODUCTION

Here we explore the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of GBT021601 in healthy volunteers and adults living with sickle cell disease (SCD).

SCD is an inherited, lifelong disorder characterized by sickle hemoglobin (HbS) polymerization, resulting in red blood cell (RBC) sickling, RBC destruction, vaso-occlusion, and end-organ damage.[1]

Voxelotor is a first-in-class HbS polymerization inhibitor indicated in the United States for adult and adolescent patients (aged ≥12 years) with SCD. In the pivotal HOPE study, treatment with voxelotor resulted in rapid, robust, and sustained improvements in hemoglobin and hemolysis.[2-5]

GBT021601 is a potent, next-generation HbS polymerization inhibitor that has the potential to achieve higher hemoglobin (Hb) occupancies at lower doses than voxelotor. In an in vivo SCD mouse model, GBT021601 treatment led to substantial improvements in hematological parameters.[6]

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DISCLOSURES

Clark Brown
- Consultant: Global Blood Therapeutics, Imara, Novartis, Novo Nordisk
- Research support: Global Blood Therapeutics, Forma Therapeutics, Imara, Novartis, Pfizer

Andrew Redfern
- Employee: Linear Clinical Research
- Advisory board member: Novartis, Pfizer, Roche, Eisai, AstraZeneca

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Carla Washington
- Clinical consultant
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Irene Agodoa
- Employee, equity ownership: Global Blood Therapeutics

Kim Smith-Whitley
- Employee, equity ownership: Global Blood Therapeutics

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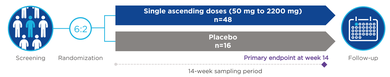
RESULTS

Healthy Volunteers Study – Single Ascending Dose

Design for Healthy Volunteers Study – Single Ascending Dose

Phase 1, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and tolerability of single ascending doses of GBT021601 in healthy volunteers.



Patient population
- Healthy volunteers aged 18 to 55 years

Primary endpoint
- Safety and tolerability

Key secondary endpoints
- PK
- Effect of food

PK, pharmacokinetics.

Healthy Volunteers SAD Cohorts: Demographics and Baseline Characteristics Were Similar Across Groups[a]

	50 mg (n=8)	100 mg (n=8)	200 mg (n=8)	200 mg (fed)[b] (n=8)	400 mg (n=8)	800 mg (n=8)	1400 mg (n=8)	2200 mg (n=8)
Mean age, years (SD)	33.3 (5.1)	28.5 (10.5)	26.5 (9.6)	26.5 (9.8)	34.4 (11.3)	34.1 (10.9)	29.6 (8.0)	25.4 (4.7)
Male, n (%)	8 (100)	7 (87.5)	8 (100)	8 (100)	6 (75.0)	7 (87.5)	7 (87.5)	8 (100)
Race, n (%)								
White	4 (50.0)	5 (62.5)	6 (75.0)	6 (75.0)	2 (25.0)	6 (75.0)	7 (87.5)	5 (62.5)
Asian	3 (37.5)	2 (25.0)	1 (12.5)	2 (25.0)	5 (62.5)	0	1 (12.5)	1 (12.5)
Black or African American	0	0	0	0	0	1 (12.5)	0	0
Other	1 (12.5)	1 (12.5)	1 (12.5)	0	1 (12.5)	1 (12.5)	0	2 (25.0)

[a]All groups consisted of 6 healthy volunteers who received voxelotor and 2 healthy volunteers who received placebo. [b]To determine food effect, 200 mg dose was given in fasting state and after a high-fat meal.
SAD, single ascending dose.

Healthy Volunteers SAD Cohorts: Most TEAEs Were Grade 1 or 2

Overview of TEAEs[a]	50 mg (n=8)	100 mg (n=8)	200 mg (n=8)	200 mg (fed)[b] (n=8)	400 mg (n=8)	800 mg (n=8)	1400 mg (n=8)	2200 mg (n=8)
Number of TEAEs	14	13	16	8	23	14	29	17
Number of participants with at least 1 TEAE, n (%)	7 (87.5)	6 (75.0)	7 (87.5)	6 (75.0)	8 (100)	6 (75.0)	8 (100)	6 (75.0)
Number of TEAEs grade ≥3	0	0	0	1	1	0	0	0
Number of drug-related TEAEs	2	1	0	0	1	3	4	4
Number of participants with at least 1 drug-related TEAE, n (%)	2 (25.0)	1 (12.5)	0	0	1 (12.5)	2 (25.0)	4 (50.0)	2 (25.0)
Number of TEAEs leading to study drug discontinuation	0	0	0	0	0	0	0	0
Number of SAEs	0	0	0	0	1[c]	0	0	0

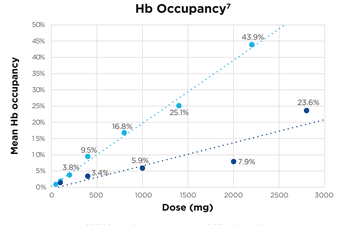
[a]As the study is currently ongoing, data presented are still blinded. [b]To determine food effect, 200 mg dose was given in fasting state and after a high-fat meal.
[c]The 1 SAE was a traumatic brain injury and was not drug related.
SAD, single ascending dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Favorable Whole Blood PK Parameters and Hemoglobin Occupancy after Single Ascending Dose per Cohort

Parameter, mean	HV 50 mg	HV 100 mg	SCD 100 mg	HV 200 mg	HV 400 mg	HV 800 mg[a]	HV 1400 mg[a]	HV 2200 mg[a]
$t_{1/2}$, days (CV%)	28 .9 (8.4)	29.8 (22.3)	9.8 (14.7)	28.4 (15.6)	25.8 (10.8)	ND	ND	ND
C_{max}, µg/mL (CV%)	8.1 (16.9)	17.4 (10.8)	16.7 (23.3)	35.8 (32.4)	88.1 (11.1)	149.3 (10.5)	231.2 (12.6)	389.7 (12.0)
AUC_{0-24}, µg·h/mL (CV%)	6896 (21.5)	14,400 (14.7)	4690 (26.8)	29,290 (26.1)	61,920 (9.3)	74,330 (4.5)	136,900 (7.8)	48,010 (10.0)
t_{max},[c] h (range)	24 (4, 48)	24 (8, 48)	8 (6, 36)	8 (4, 48)	8 (4, 120)	16 (1, 96)	12 (8, 48)	24 (12, 24)
B:P ratio[d]	220	214	69.3	206	185	ND	ND	ND
% Hb occupancy based on C_{max} (CV%)	0.88 (16.7)	1.9 (13.3)	3.3 (26.1)	3.8 (33.0)	9.5 (22.6)	16.8 (10.4)	25 (12.4)	43.9 (12.3)

[a]Blood collected up to day 42. [b]Blood collected up to day 7 (study still ongoing). [c]t_{max} reported as median. [d]B:P = mean $AUC_{0-t\ blood}$/mean $AUC_{0-t\ plasma}$.
AUC_{0-t}, area under the curve to last measurable concentration time; C_{max}, maximal observed concentration; CV, coefficient of variation; Hb, hemoglobin; HV, healthy volunteer; ND, not determined; PK, pharmacokinetics; SCD, sickle cell disease; $t_{1/2}$, half-life; t_{max}, time of maximal observed concentration.

Single Doses of GBT021601 Showed a Dose-Dependent Increase in Percent Hb Occupancy in Healthy Volunteers

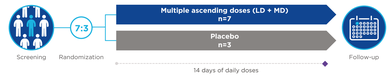


Hb, hemoglobin.
- There was no observable difference in Hb occupancy between fasting and fed states (200 mg).
- These Hb occupancies exceed those reported in healthy volunteers receiving single doses of voxelotor over a similar range.[8]

Healthy Volunteers Study – Multiple Ascending Dose

Design for Healthy Volunteers Study – Multiple Ascending Dose

Ongoing phase 1, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and pharmacological effects of multiple ascending doses of GBT021601 in healthy volunteers.



Patient population
- Healthy volunteers aged 18 to 55 years

Primary endpoint
- Safety and tolerability

One dose cohort to date
- LD: 300 mg × 3 days
  MD: 15 mg × 11 days

Key secondary endpoints
- PK
- Effect on ECG parameters

ECG, electrocardiogram; LD, loading dose; MD, maintenance dose; PK, pharmacokinetics.

Healthy Volunteers 15 mg MAD Cohort: Demographics and TEAEs

Demographics	15 mg maintenance (n=10)
Mean age, years (SD)	43.7 (9.12)
Male, n (%)	6 (60.0)
Race n (%)	
White	7 (70.0)
Black or African American	3 (30.0)

Overview of TEAEs[a]	15 mg maintenance (n=10)
Number of TEAEs	5
Number of participants with at least 1 TEAE, n (%)	4 (40.0)
Number of TEAEs grade ≥3	0
Number of drug-related TEAEs	1[b]
Number of participants with at least 1 drug-related TEAE, n (%)	1 (10.0)
Number of TEAEs leading to study drug discontinuation	0
Number of SAEs	0

[a]As the study is currently ongoing, data presented are still blinded. [b]The 1 drug-related TEAE was grade 1 somnolence in 1 participant.
MAD, multiple ascending dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Preliminary Whole Blood PK Parameters and Hemoglobin Occupancy in Healthy Volunteers 15 mg MAD Cohort[7]

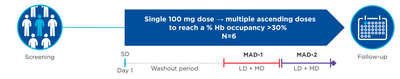
Parameter,[a] mean	Day 14 (15 mg)
C_{max}, µg/mL (CV%)	130.7 (14.3)
t_{max},[b] h (range)	6 (0.5-24)
AUC_{0-24}, µg·h/mL (CV%)	2865 (13.7)
B:P ratio[c]	182.4
% Hb occupancy (CV%)	16.0[d] (14.3)

[a]Calculations based on nominal (anticipated) collection times, not actual. [b]t_{max} reported as median. [c]B:P = mean $AUC_{0-24\ blood}$/mean $AUC_{0-24\ plasma}$. [d]To achieve a similar Hb occupancy with voxelotor, more than 300 mg MAD was needed.[7]
AUC_{0-24}, area under the curve to 24 hours post-dose; C_{max}, maximal observed concentration; CV, coefficient of variation; Hb, hemoglobin; MAD, multiple ascending dose; PK, pharmacokinetics; SCD, sickle cell disease; $t_{1/2}$, half-life; t_{max}, time of maximal observed concentration.

Adults Living with SCD Study

Design for Adults Living with SCD Study

Ongoing phase 1, single-arm, intrapatient single-dose and multiple-ascending-dose trial to evaluate the safety and efficacy of GBT021601 in adults with SCD.



Patient population
- Patients with HbSS, aged 18 to 60 years
- Baseline Hb ≥5.5 g/dL and ≤10.5 g/dL
- No VOCs or transfusions within 30 days of screening

Primary endpoint
- Safety and tolerability

Key secondary endpoints
- PK
- Relationship between time-matched GBT021601 concentrations and the changes in clinical measures of anemia and hemolysis from baseline

Hb, hemoglobin; HbSS, homozygous for SCD; LD, loading dose; MAD, multiple ascending dose; MD, maintenance dose; PK, pharmacokinetics; SCD, sickle cell disease; SD, single dose; VOC, vaso-occlusive crisis.

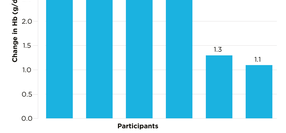
SCD Cohort: Demographics and TEAEs

Demographics and baseline characteristics	SCD (N=6)
Mean age, years (SD)	20.2 (2.23)
Male, n (%)	4 (66.7)
Race, n (%)	
Black or African American	5 (83.3)
Other	1 (16.7)
HbSS genotype, n (%)	6 (100)
Current hydroxyurea use, n (%)	6 (100)
Number of VOCs within 12 months of screening	
0	2 (33.3)
1	1 (16.7)
2	3 (50.0)
Number of transfusions within 12 months of screening	
0	4 (66.7)
1	2 (33.3)

Overview of TEAEs[a]	SCD (N=6)
Number of TEAEs	24
Number of participants with at least 1 TEAE, n (%)	5 (83.3)
Number of TEAEs grade ≥3	5
Number of drug-related TEAEs	3[b]
Number of participants with at least 1 drug-related TEAE, n (%)	2 (33.3)
Number of TEAEs leading to study drug discontinuation	0
Number of SAEs	2[c]

[a]As the study is currently ongoing, data cutoff is as of December 6, 2021. [b]The drug-related TEAEs were grade 2 headache and 2 cases of grade 1 diarrhea. [c]The 2 SAEs were grade 3 VOCs.
HbSS, homozygous for SCD; SAE, serious adverse event; SCD, sickle cell disease; TEAE, treatment-emergent adverse event; VOC, vaso-occlusive crisis.

Per-Patient Change in Hb and Hb Occupancy at Day 112

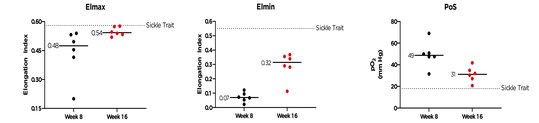


Participants	Hb occupancy (%) at week 16, apparent C_{max}
01018-0001	41.12
01018-0003	41.81
01018-0004	29.57
01018-0005	38.84
01018-0006	19.67
01018-0007	24.52
N	6
Mean	32.59
SD	9.35
CV%	28.7

Mean values are consistent with those observed at weeks 14 and 15. The data suggests dose proportionality in Hb occupancy (%) in relation to cohort 1 data.

[a]Baseline Hb was at day 56 after washout period and at start of MAD.
C_{max}, maximal observed concentration; CV, coefficient of variation; Hb, hemoglobin; MAD, multiple ascending dose; SD, standard deviation.

Lorrca Oxygenscan with Improved Elongation Index at Week 16



El_{max}, maximum elongation index; El_{min}, minimum elongation index; pO_2, partial pressure of oxygen. PoS, point of sickling.

CONCLUSIONS

Single doses and multiple daily doses of GBT021601 are well tolerated in healthy volunteers and adults living with SCD, with studies currently ongoing. Preliminary single-dose data of GBT021601 showed a linear dose-dependent increase in percent Hb occupancy up to the highest dose evaluated, 2200 mg.

GBT021601 has the potential to achieve a targeted Hb occupancy and attain desired hematological effects at lower doses than voxelotor, therefore reducing pill burden and improving clinical outcomes for individuals living with SCD.

Further multiple-dose data will help evaluate GBT021601's potential as a best-in-class, oral, disease-modifying therapy for SCD.

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