Preliminary Results of a Phase 1 Study in Healthy Subjects Administered Inclacumab, a Fully Human IgG4 Anti-P-Selectin Monoclonal Antibody in Development for Treatment of Sickle Cell Disease

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BACKGROUND

Inclacumab Is Being Developed for the Management of Vaso-Occlusive Crises in Patients with Sickle Cell Disease[1,2]

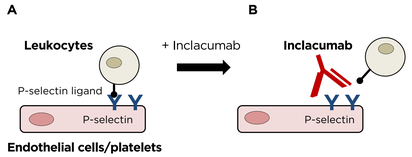
Inclacumab, a fully human immunoglobin G4 (IgG4) anti-P-selectin monoclonal antibody (mAb), is under investigation as a potential treatment to reduce the frequency of vaso-occlusive crises (VOCs) and hospital readmissions for VOCs in patients with sickle cell disease (SCD).[1-3]

Safety and pharmacology of intravenous (IV) inclacumab have previously been well characterized in more than 700 individuals, including both healthy volunteers and patients with cardiovascular disease, at doses up to 20 mg/kg every 4 weeks.[4-6]

A phase 1 study was initiated to evaluate the safety and pharmacology of a single IV dose of inclacumab at 20 mg/kg and 40 mg/kg in healthy participants in support of a target phase 3 dose of 30 mg/kg administered every 12 weeks to patients with SCD.[1]

Here we report the safety, pharmacokinetics (PK), anti-drug antibody (ADA), and ex vivo platelet-leukocyte aggregate (PLA) formation results for the phase 1 study of inclacumab.

Mechanism of Action of Inclacumab[7-9]



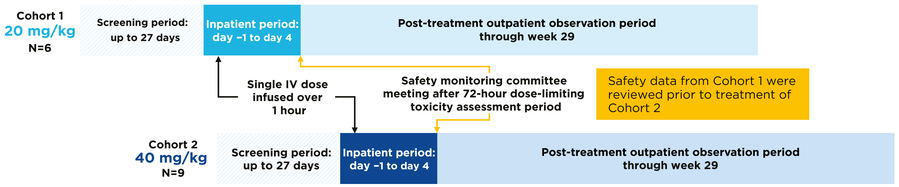
A. P-selectin is a cell adhesion molecule produced by endothelial cells and platelets. Upon activation of these cells, P-selectin is translocated to the cell surface where it mediates leukocyte recruitment by binding to its primary ligand, P-selectin glycoprotein ligand-1 (PSGL-1). The same mechanism is also responsible for abnormal rolling and adhesion of sickle red blood cells to the endothelium, initiating acute vascular occlusion and chronically impairing microvascular blood flow in patients with SCD.

B. Inclacumab binds to P-selectin, blocking its interaction with PSGL-1 and subsequently inhibiting leukocyte adhesion to platelets and endothelial cells.

METHODS

Two Cohorts of Healthy Adults Were Enrolled in This Open-Label, Single-Ascending-Dose Study of Inclacumab[a]

OBJECTIVE: To evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of a single dose of inclacumab in healthy adults ≥18 years of age.



[a]The protocol was conducted in Australia under Ethics Committee approval.
IV, intravenous.

RESULTS

Summary of Demographics and Baseline Characteristics

	Cohort 1 Inclacumab 20 mg/kg (N=6)	Cohort 2 Inclacumab 40 mg/kg (N=9)	Pooled Inclacumab (N=15)
Age, years			
Mean (SD)	33.5 (8.41)	40.3 (9.86)	37.6 (9.63)
Median (minimum, maximum)	30.5 (25, 44)	43.0 (22, 52)	42.0 (22, 52)
Sex, n (%)			
Female	3 (50.0)	4 (44.4)	7 (46.7)
Male	3 (50.0)	5 (55.6)	8 (53.3)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	6 (100)	9 (100)	15 (100)
Race, n (%)			
Asian	2 (33.3)	2 (22.2)	4 (26.7)
White	4 (66.7)	6 (66.7)	10 (66.7)
Other (White/Kiwi/Pacific Islander)	0	1 (11.1)	1 (6.7)
Baseline weight, kg			
Mean (SD)	69.4 (4.78)	78.1 (8.76)	74.6 (8.46)
Median (minimum, maximum)	68.9 (63.7, 75.4)	79.2 (66.2, 89.3)	73.6 (63.7, 89.3)

Inclacumab Was Well Tolerated for the 29-Week Duration of the Study

	Cohort 1 Inclacumab 20 mg/kg (N=6)	Cohort 2 Inclacumab 40 mg/kg (N=9)
72-hour post-infusion safety assessments, n (%)		
TEAEs grade >1	0	0
Infusion-related reactions	0	0
Hypersensitivity reactions	0	0
Dose-limiting toxicities	0	0
TEAEs reported in >1 subject in respective cohort, n (%)		
Upper respiratory tract infections	—	4 (44.4)
Headache	2 (33.3)	4 (44.4)
Myalgia	—	3 (33.3)
Back pain	—	2 (22.2)
Contact dermatitis	—	2 (22.2)
Serious TEAEs, n (%)	0	0
TEAEs potentially related to inclacumab, n (%)		
Headache	1 (16.7)	0
Dizziness	1 (16.7)	0

TEAE, treatment-emergent adverse event.

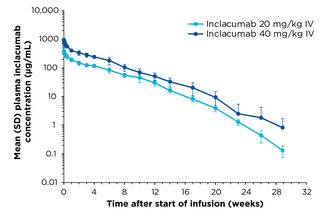
- No clinically significant changes in vital signs, laboratory findings, or electrocardiograms were observed.
- The only treatment-emergent adverse events assessed by the investigator as potentially related to inclacumab were headache and dizziness, which were experienced by 1 subject in Cohort 1 and occurred 4 hours after end of infusion.

Plasma Inclacumab Concentration–Time Profiles Demonstrated Expected mAb PK for Healthy Subjects

Plasma Inclacumab Concentration–Time Profiles[a]

- Plasma inclacumab concentrations decreased in a multiphasic manner.
- Apparent nonlinearity was observed in the majority of subjects below approximately 10 µg/mL, indicating the likely contribution of target-mediated drug disposition (TMDD).

[a]Quantification of free plasma inclacumab was performed using a validated electrochemiluminescence assay with a lower limit of quantification of 10 ng/mL.
IV, intravenous; mAb, monoclonal antibody; PK, pharmacokinetics.



Inclacumab IV PK Parameters[a]

PK parameter	Cohort 1 Inclacumab 20 mg/kg (N=6) Geometric mean (geometric CV%)	Cohort 2 Inclacumab 40 mg/kg (N=9) Geometric mean (geometric CV%)
C_{max}, µg/mL	402 (10.1)	970 (17.9)
t_{max}, h[b]	2.01 (1.00, 7.02)	1.03 (1.00, 25.0)
$AUC_{0\text{-}inf}$, day·µg/mL	8920 (15.2)	19,100 (14.7)
$t_{1/2}$, day	13.2 (13.0)	15.2 (52.5)
C_{12w}, µg/mL	27.4 (20.3)	48.5 (34.2)

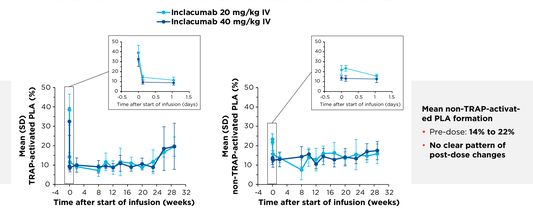
[a]PK parameters were calculated using validated Phoenix™ WinNonlin software (version 8.3). [b]Median (minimum – maximum) is presented.
$AUC_{0\text{-}inf}$, area under the curve from time 0 to infinity; C_{12w}, concentration at 12 weeks; C_{max}, maximum concentration; CV, coefficient of variation; IV, intravenous; PK, pharmacokinetics; $t_{1/2}$, terminal elimination half-life; t_{max}, time of maximum concentration (from start of 1-hour infusion).

- Plasma inclacumab exposure (C_{max} and $AUC_{0\text{-}inf}$) increased dose proportionally over the dose range tested.
- $t_{1/2}$ calculated by noncompartmental analysis was 13.2 days and 15.2 days at 20 mg/kg and 40 mg/kg, respectively.
- C_{12w} was greater than the target activity threshold of 10 µg/mL at both doses, which was associated with full inhibition of PLA formation in prior phase 1 and 2 studies of inclacumab.

Maximal Inhibition of TRAP-Activated PLA Formation Was Sustained up to 23 Weeks at Both Doses Tested

TRAP- and Non-TRAP-Activated PLA Formation vs Time Profiles[a]

Mean TRAP-activated PLA formation
- Pre-dose: **33% to 39%**
- EOI + 2 h: **9% to 14%**
- Mean reduction from baseline over 23 weeks: **~20% to 30%**



Mean non-TRAP-activated PLA formation
- Pre-dose: **14% to 22%**
- **No clear pattern of post-dose changes**

[a]Under normal physiological conditions, few platelets are activated and express P-selectin; therefore, the percentage of PLAs is relatively small. Addition of TRAP ex vivo activates the platelets by upregulating P-selectin on the platelet surface, resulting in robust PLA formation, allowing for better observation of PLA modulation by inclacumab.
EOI, end of infusion; IV, intravenous; PLA, platelet-leukocyte aggregate; TRAP, thrombin receptor–activating peptide.

Treatment-Emergent ADA Developed in 2 of 15 Healthy Subjects Following a Single Dose of Inclacumab with No Apparent Impact on Safety or PK/PD

		Confirmatory Assay Results[a]		
	Time (weeks)	No. of ADA samples	ADA-negative n (%)	ADA-positive n (%)
Cohort 1 Inclacumab 20 mg/kg (N=6)	0 (pre-dose)	6	6 (100)	0
	6	6	6 (100)	0
	12	6	6 (100)	0
	26	5	5 (100)[b]	0[b]
	29	5	5 (100)[b]	0[b]
Cohort 2 Inclacumab 40 mg/kg (N=9)	0 (pre-dose)	9	9 (100)	0
	6	9	9 (100)	0
	12	9	7 (77.8)	2 (22.2)
	26	9	7 (77.8)	2 (22.2)
	29	9	7 (77.8)	2 (22.2)

[a]Immunogenicity was assessed using a validated bridging ADA assay. [b]One subject had no sample at the week 26 and week 29 time points.
ADA, anti-drug antibody; PD, pharmacodynamics; PK, pharmacokinetics.

- There were no confirmed ADA-positive samples at baseline.
- The incidence of treatment-emergent ADA was 0% (0 of 6) in Cohort 1 and 22% (2 of 9) in Cohort 2, and the time to ADA development in the ADA-positive subjects was 12 weeks.
- Both ADA-positive subjects demonstrated persistent ADA for the remainder of the 29-week observation period.
- No unique safety signals and no clear impacts on PK or PD were observed in the 2 ADA-positive subjects.

CONCLUSIONS

Inclacumab showed a well-tolerated safety profile for up to 29 weeks after a single dose of 20 mg/kg or 40 mg/kg in healthy subjects.

Plasma inclacumab exposures were dose proportional over the dose range tested, with apparent nonlinearity below approximately 10 µg/mL, suggestive of TMDD.

Persistent inhibitory activity of ex vivo TRAP-activated PLA formation was observed up to 23 weeks after a single intravenous inclacumab dose of 20 mg/kg or 40 mg/kg.

Overall, the results support a phase 3 dose of 30 mg/kg every 12 weeks in patients with SCD experiencing VOCs. Global Blood Therapeutics is currently enrolling and treating patients with SCD in phase 3 clinical studies of inclacumab.[1,2,10,11]

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DISCLOSURES

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- Owner and principal consultant: Semivida Research, LLC
- Consultant: Global Blood Therapeutics
- Former employee: Global Blood Therapeutics

Daniel Cooper
- Nothing to disclose

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