Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Briquilimab After Single Subcutaneous (SC) Administration to Healthy Male and Female Participants

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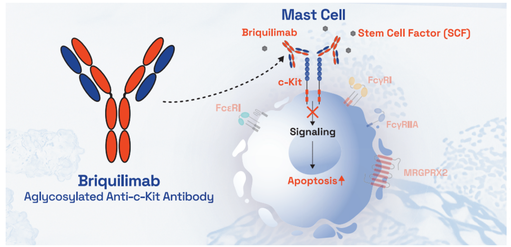
BACKGROUND



- Aglycosylated monoclonal antibody the binds to cell-surface receptor c-Kit (CD117), inhibiting stem cell factor binding/signaling through the receptor
- Blocks key survival signals leading to apoptosis

STUDY DESIGN AND POPULATION

- Placebo-controlled, randomized, double-blind, ascending dose study
- Healthy men and women between 18 and 60 years old
- BMI between 18 and 35 kg/m^2
- A single dose of briquilimab administered subcutaneously (SC) or intravenously (IV)

METHODS

Safety (Primary Endpoint)

- Incidence of adverse events (AEs), clinical laboratory values, ECGs and immunogenicity by collection of serum samples at predose and end of study

Pharmacodynamics (Secondary Endpoints)

- PD characterized by drug's ability to inhibit recruitment of new mast cells (MCs) in a cutaneous wound model after SC administration of 10 mg and at higher dose levels
- Subjects received 4 punch biopsies: 2 pre-dose (3 mm each); 6 days post-dose (6 mm each); 28 days post-dose (6 mm)
- Skin mast cells assessed by 1) count of CD117-positive mast cells; 2) cytometry assay to measure tryptase-positive cells

Pharmacokinetics (Secondary Endpoints)

- Serial serum samples were collected for 28 days (dose levels ≤5 mg), 56 days (dose levels between 10 and 158 mg, inclusive) or 70 days (280 mg) after dosing

All evaluated doses*

0.2 mg SC → 0.7 mg SC → 2 mg SC → 5 mg SC → 10 mg SC → 20 mg SC → 5 mg IV → 42 mg SC → 84 mg SC → 158 mg SC → 280 mg SC

*SC dosing cohort endpoints informed dose selection / design of ongoing urticaria clinical trials; therefore, results from relevant SC dosing cohorts (≥ 42 mg) are presented here.

Briquilimab is an investigational product and not approved for any indication.

[a]Defined as ≥ 10% of subjects and more than twice as frequent following drug than placebo.

[b]Data from this study was used to inform the selection of doses and schedules currently being evaluated in the BEACON and SPOTLIGHT clinical trials in CSU and CIndU patients (NCT06162728 and NCT06353971, respectively).

References: 1. Jasper internal data (Phase 1a, healthy volunteer study) **2.** Maurer et al, GA²LEN Global Urticaria Forum; Berlin, December 6, 2022

SUBJECT DEMOGRAPHICS AND DISPOSITION

		Placebo	Briquilimab cohorts
Number of subjects		25	71
Sex	Female	9	37
	Male	16	34
Ethnicity/race	White	22	67
	Black	0	1
	Asian	1	1
	Other	2	2
Age, median [range]		54 [38 – 59] years	51 [35 – 60] years
BMI, median [range]		27 [23 – 36] kg/m^2	27 [19 – 35] kg/m^2

95 out of 96 subjects completed the study. One subject at the 42 mg briquilimab dose level withdrew consent and discontinued from the study.

SAFETY

Table 2. Summary (number of subjects (% of subjects)) of treatment related adverse events in ≥ 5% of subjects after administration of briquilimab 10 mg to 280 mg SC

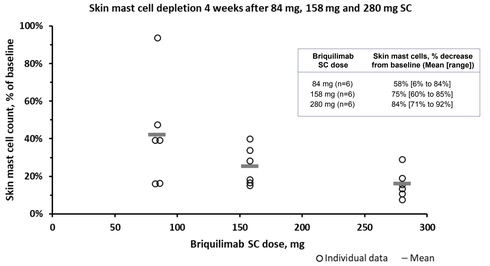
	Placebo (n=25)	Briquilimab SC dose, mg: 10 mg (n=6)	20 mg (n=6)	42 mg (n=12)	84 mg (n=6)	158 mg (n=6)	280 mg (n=6)
At least 1 adverse event	18 (72)	6 (100)	6 (100)	10 (83)	3 (50)	6 (100)	5 (83)
Headache	10 (40)	3 (50)	4 (67)	5 (42)	0 (0)	5 (83)	2 (33)
Nausea	2 (8)	2 (33)	0 (0)	2 (17)	0 (0)	2 (33)	2 (33)
Upper respiratory tract infection	0 (0)	1 (17)	2 (33)	2 (17)	1 (17)	1 (17)	0 (0)
Lethargy	1 (4)	1 (17)	1 (17)	0 (0)	0 (0)	1 (17)	0 (0)
Dizziness	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dysgeusia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (83)
Impaired healing	1 (4)	5 (83)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	2 (17)	0 (0)	1 (17)	1 (17)

AEs in 94 of 96 subjects. All treatment-emergent AEs either mild or moderate and no Grade ≥3 AEs, serious AEs or deaths.

- Nausea, upper respiratory tract infection, dizziness, back pain, and lethargy most common AEs with briquilimab.[a] No clear association with briquilimab dose observed
- Dysgeusia in 5/6 subjects after 280 mg dose: mild or moderate and reversible
- Escalation to the final planned dose level of 420 mg was not conducted due to dysgeusia at 280 mg and because no additional PD effect was observed at 280 mg

BRIQUILIMAB MOA

Single subcutaneous injection of briquilimab significantly depletes human skin MCs[1,2]

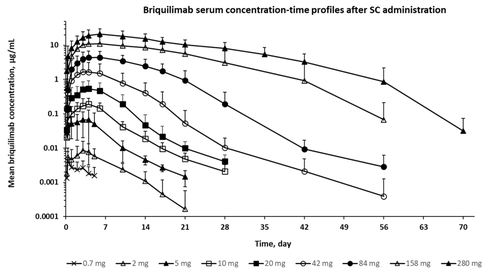


- SC dose ≥ 84 mg potently depletes skin MCs in dose-dependent fashion
- MC depletion by day 7, with durable response lasting at least 29 days
- MCs take at least 3 months to recover, potentially leading to durable disease control[2]

ANTI-BRIQUILIMAB ANTIBODIES

- 10/71 evaluated subjects (14%) positive for treatment-emergent binding anti-briquilimab antibodies (anti-drug antibodies, ADA)
- All 10 subjects dosed at 20 mg or higher; no clear association evident between ADA and dose
- 6/10 (3 at 42 mg and 3 at 84 mg) positive for neutralizing ADA
- Neutralizing ADA had inconsistent effect on the results of the cutaneous wound model. Binding, non-neutralizing antibodies had no apparent impact in this wound model in any subjects

PHARMACOKINETICS



Serum concentrations <LLOQ at 0.2 mg dose level; profiles at other dose levels were indicative of nonlinear kinetics likely due to target mediated clearance.

Table 1. Mean (%CV) briquilimab PK parameters after subcutaneous administration

	Briquilimab SC dose: 0.7 mg	2 mg	5 mg	10 mg	20 mg	42 mg	84 mg	158 mg	280 mg
n	5	6	9	6	6	12	6	6	6
C_{max}, µg/mL	0.00539 (53%)	0.00862 (84%)	0.0917 (61%)	0.192 (49%)	0.569 (67%)	1.79 (89%)	4.51 (50%)	11.3 (55%)	21.3 (39%)
T_{max}, day [A]	0.33 [0.33-1.0]	3.5 [3.0-5.0]	3.0 [0.17-4.0]	3.5 [3.0-4.0]	3.5 [3.0-6.5]	4.0 [1.0-6.5]	4.0 [4.0-6.0]	6.5 [2.0-10]	6.2 [6.0-6.5]
AUC_{last}, µg*day/mL	0.0142 (36%)	0.0606 (59%)	0.480 (74%)	1.48 (44%)	4.53 (67%)	18.5 (93%)	64.6 (56%)	243 (73%)	511 (46%)

In clinically relevant dose range of ≥84 mg, max serum concentrations typically observed 4-6 days after SC administration.

More than dose proportional increase in serum exposure in the dose range evaluated; serum exposure was nearly dose proportional after administration of 158 mg and 280 mg.

CONCLUSIONS

- SC briquilimab safe and well tolerated up to highest dose evaluated (280 mg)
- All AEs mild or moderate
- Changes in clinical laboratory values reversible
- SC briquilimab had predictable PK / PD
  - MC depletion in cutaneous wound model durable and dose-dependent.
  - Threshold for MC depletion was drug exposure > 0.8 mg/kg
- Low incidence of ADA, no effect on PD
- PK and PD effects may enable optimal biologic dosing for treatment of mast cell mediated disease[b]