CLINICAL PHARMACOKINETICS AND IMMUNOGENICITY OF GBR 830, A FIRST-IN-CLASS HUMANIZED MONOCLONAL ANTIBODY INHIBITING OX40 TO TREAT ATOPIC DERMATITIS

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ABSTRACT

GBR 830 is a first-in-class, humanized, monoclonal IgG1 antibody that specifically inhibits OX40, a costimulatory receptor on activated T cells. Three studies have been completed to evaluate the pharmacokinetics (PK) and immunogenicity of GBR 830. A single ascending dose study with GBR 830 (0.3, 1, 3, and 10 mg/kg) by intravenous (IV) infusion was conducted in healthy volunteers. GBR 830 was well tolerated with no clinically significant findings. GBR 830 showed linear PK with dose proportional increases in C_{max} and AUC. An early C_{max} (median T_{max} 1.5-4 hours) and a bi-exponential decline with a long terminal elimination phase ($T_{1/2}$ 10-15 days) was observed without discernable influence of target-mediated clearance. Six of 34 GBR 830-treated subjects were positive for anti-drug antibody (ADA), 2 of whom had neutralizing ADA. An absolute bioavailability (%F) study was conducted in healthy adults with a single dose of GBR 830 by IV (600 mg/subject) or subcutaneous (SC) administration (75 or 600 mg/subject). The %F of GBR 830 by the SC route was ~65%, with C_{max} achieved around 5 days post-dose. A lower incidence of ADA was observed with higher doses (600 mg SC: 1/15 subjects; 600 mg IV: 1/10 subjects) compared to the lower dose (75 mg SC: 10/15 subjects). PK of GBR 830 was also evaluated in subjects with moderate-to-severe atopic dermatitis (AD) (NCT02683928). Two IV doses of GBR 830 (10 mg/kg; 4 weeks apart) in subjects with AD showed minimal accumulation in $AUC_{0\text{-}tau}$ (1.22-fold). Six of 46 GBR 830-treated AD subjects were ADA positive. In conclusion, GBR 830 was well tolerated and showed a similar PK profile in healthy volunteers and subjects with AD. A favorable linear PK profile with a long half-life, high bioavailability, and no evidence of target-mediated disposition was observed. ADA generation had no discernable effect on PK and safety.

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RESULTS

Single Ascending Dose Study in Healthy Subjects

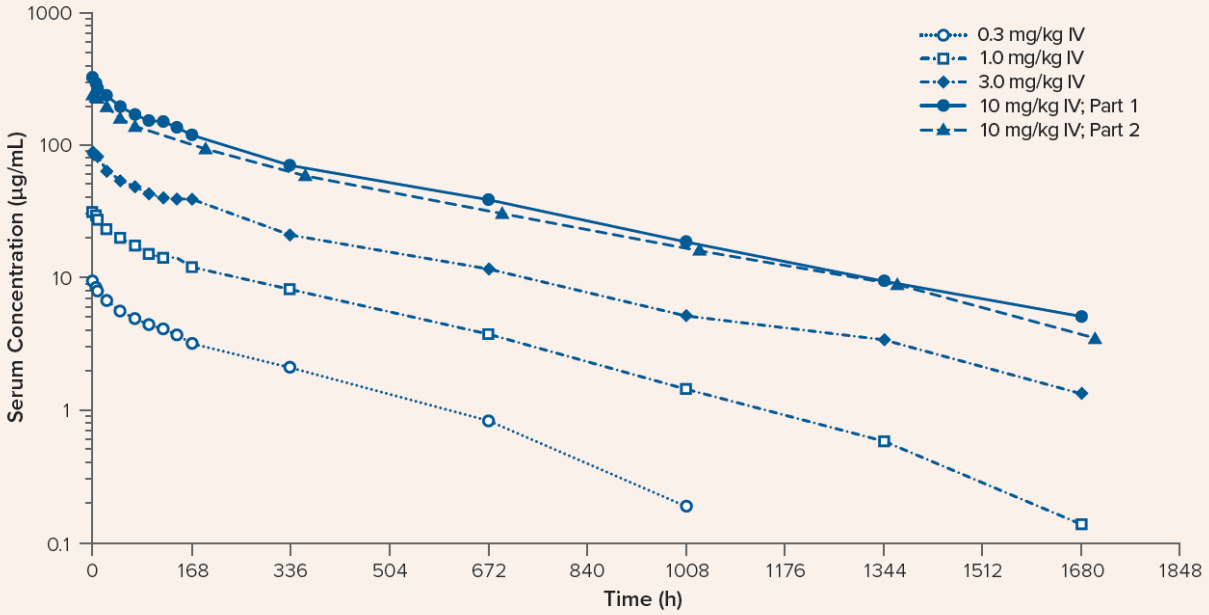
- In this two-part, phase 1 study that included 52 healthy adult volunteers (GBR 830, n=34; placebo, n=18), GBR 830 showed linear PK with dose-proportional increases in C_{max} and AUC (**Table 1; Figure 1**)

Table 1. Mean PK Parameters of GBR 830 in Healthy Subjects Following 1-Hour IV Infusion

PK Parameter[a]	Part 1				Part 2
	0.3 mg/kg (n=6)	1 mg/kg (n=6)	3 mg/kg (n=6)	10 mg/kg (n=6)	10 mg/kg (n=10)
C_{max}, µg/mL	9.5 (26.6)	33.8 (11.8)	94.7 (12.9)	339 (22.0)	271 (11.4)
T_{max}, h	2.0 (1.0-6.0)	4.0 (1.02-6.0)	1.8 (1.0-8.0)	2.0 (1.5-4.0)	2.0 (1.5-4.0)
$AUC_{0\text{-}tlast}$, µg·h/mL	1910 (33.5)	7820 (15.5)	23956 (23.7)	79125 (19.9)	68957 (16.1)
$AUC_{0\text{-}\infty}$, µg·h/mL	2052 (31.8)	7938 (15.4)	24970 (26.4)	81929 (20.7)	71277 (17.6)
CL, L/h	0.0117 (17.2)	0.0096 (17.7)	0.00933 (28.2)	0.0084 (34.5)	0.0114 (18.3)
V_{SS}, L	3.90 (13.7)	3.58 (20.7)	4.42 (11.7)	3.82 (30.2)	5.21 (14.2)
V_Z, L	4.02 (9.07)	3.43 (19.4)	4.82 (15.5)	4.32 (25.0)	5.65 (15.7)
$t_{1/2}$, h	238 (17.6)	247 (14.2)	358 (29.8)	356 (15.2)	344 (18.3)

[a] Geometric mean (% coefficient of variation geometric mean) is provided for all PK parameters except for T_{max}; T_{max} data are presented as median (min-max). $AUC_{0\text{-}\infty}$, area under the serum concentration-time curve to infinity; $AUC_{0\text{-}tlast}$, area under the serum concentration-time curve to the last observed time point; CL, clearance; C_{max}, maximum concentration; h, hours; IV, intravenous, PK, pharmacokinetic; $t_{½}$, terminal elimination half-life; T_{max}, time to C_{max}; V_{ss}, volume of distribution at steady state; V_z, volume of distribution based on the terminal elimination phase.

Figure 1. GBR 830 Geometric Mean Serum Concentration-Time Profile in Healthy Subjects



Serum concentration was quantified using a validated enzyme-linked immunosorbent assay (ELISA) method (lower limit of quantitation: 97.7 ng/mL).
h, hours; IV, intravenous.

KEY FINDINGS

- Results from a validated ligand binding assay indicated that 6 GBR 830-treated subjects (and no placebo-treated subjects) were positive for anti-drug antibody (ADA; **Table 2**)
  - Two GBR 830-treated subjects had neutralizing ADA
- GBR 830 was well tolerated with no clinically significant findings

Table 2. Anti-Drug Antibody Results in Healthy Subjects

n (%)[a]	Placebo (n=18)[b]	0.3 mg/kg (n=6)	1 mg/kg (n=6)	3 mg/kg (n=6)	10 mg/kg (n=16)[b]
Negative	18 (100)	2 (33)	5 (83)	5 (83)	16 (100)
Positive	0	4 (67)	1 (17)	1 (17)	0

[a] For positive ADA status, results of the confirmatory assay were counted.
[b] Data from Part 1 and Part 2 of the study were considered.
ADA, anti-drug antibody.

Absolute Bioavailability (%F) Study in Healthy Subjects

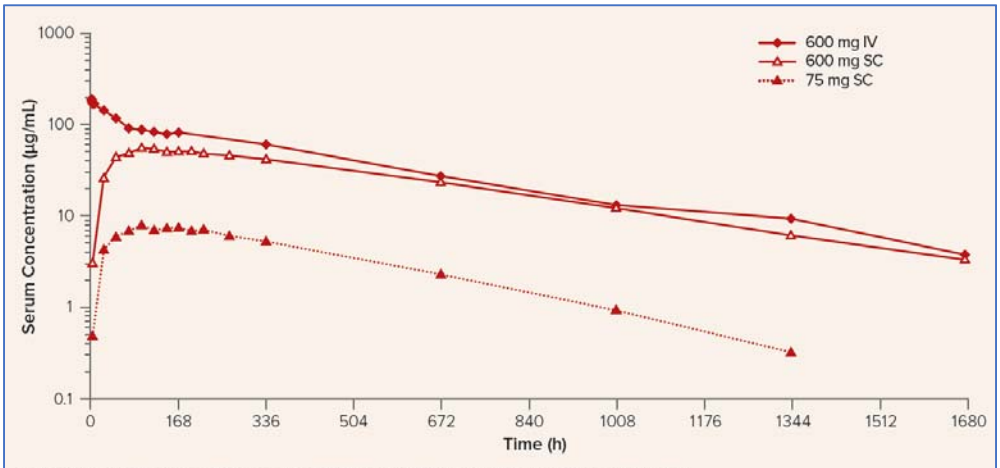
- In this phase 1 study that included 40 healthy adult volunteers with a single dose of GBR 830 by intravenous (IV) or subcutaneous (SC) administration, the %F of GBR 830 by SC injection was ~65%, with C_{max} achieved around 4 to 5 days post-dose (**Table 3; Figure 2**)

Table 3. Mean PK Parameters of GBR 830 in Healthy Subjects Following IV or SC Injection

PK Parameter[a]	600 mg IV (n=9)	600 mg SC (n=15)	75 mg SC (n=15)
C_{max}, µg/mL	191 (17.5)	59.7 (32.3)	8.59 (47.1)
T_{max}, h	2.0 (1-6)	120 (48-192)	96 (48-192)
$AUC_{0\text{-}tlast}$, µg·h/mL	56894 (14.1)	37188 (31.8)	4092 (53.4)
$AUC_{0\text{-}\infty}$, µg·h/mL	59105 (16.2)[d]	39127 (32.4)	4668 (48.4)[e]
CL, L/h[b]	0.0102 (16.2)[d]	0.0153 (32.4)	0.0161 (48.4)[e]
V_{SS}, L[c]	5.03 (14.6)[d]	NC	NC
V_Z, L[b]	5.17 (15.7)[d]	8.05 (31.4)	6.23 (49.2)[e]
$t_{1/2}$, h	353 (15.2)[d]	364 (13.6)	269 (24.8)[e]

[a] Geometric mean (% coefficient of variation geometric mean) is provided for all PK parameters except for T_{max}; T_{max} data are presented as median (min-max).
[b] CL and V_z for IV infusion, CL/F and V_z/F for SC injection.
[c] V_{ss} for IV infusion.
[d] n=8.
[e] n=13.
$AUC_{0\text{-}\infty}$, area under the serum concentration-time curve to infinity; $AUC_{0\text{-}tlast}$, area under the serum concentration-time curve to the last observed time point; CL, clearance; C_{max}, maximum concentration; F, bioavailability; h, hours; IV, intravenous; NC, not calculable; PK, pharmacokinetic; $t_{½}$, terminal elimination half-life; SC, subcutaneous; T_{max}, time to C_{max}; V_{ss}, volume of distribution at steady state; V_z, volume of distribution based on the terminal elimination phase.

Figure 2. GBR 830 Geometric Mean Serum Concentration-Time Profile in Healthy Subjects Following IV Infusion or SC Injection



Serum concentration was quantified using a validated ELISA method (lower limit of quantitation: 97.7 ng/mL).
h, hours; IV, intravenous; SC, subcutaneous.

- A lower incidence of ADA was observed with higher GBR 830 doses (**Table 4**); no discernible effect of ADA on PK or safety was observed

Table 4. Anti-Drug Antibody Results in Healthy Subjects Following GBR 830 IV Infusion or SC Injection

n (%)[a]	600 mg IV (n=10)	600 mg SC (n=15)	75 mg SC (n=15)
Negative	9 (90)	14 (93)	5 (33)
Positive	1 (10)	1 (7)	10 (67)

[a] For positive ADA status, results of the confirmatory assay were counted.
ADA, anti-drug antibody; IV, intravenous; SC, subcutaneous.

Phase 2a Proof-of-Concept Study in Moderate-to-Severe Atopic Dermatitis (AD)

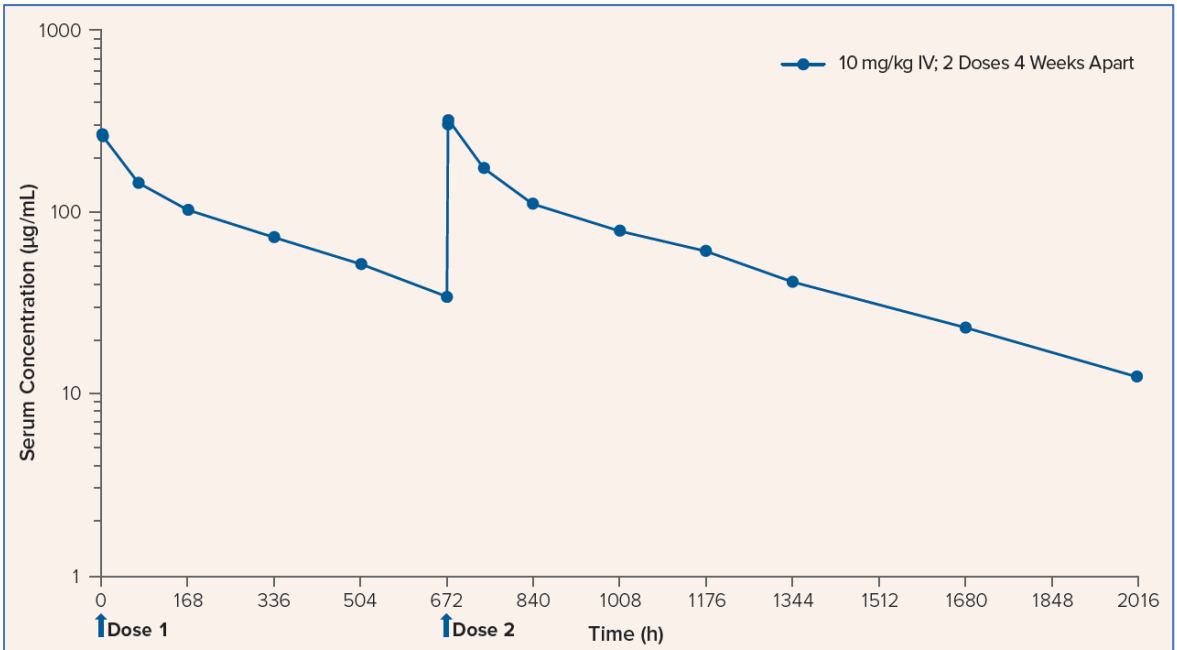
- In this randomized, double-blind, placebo-controlled, repeated dose study (NCT02683928), subjects were randomized 3:1 to GBR 830 or placebo and received 2 repeated doses (each 10 mg/kg administered IV) on Days 1 and 29 with a follow-up phase of 56 days
- Of 64 eligible AD subjects randomized to treatment, 62 received treatment (GBR 830, n=46; placebo, n=16) with minimal accumulation observed in C_{max}, C_{trough}, and $AUC_{0\text{-}tau}$ (1.16 to 1.22- fold) (**Table 5; Figure 3**)

Table 5. Mean PK Parameters of GBR 830 in Subjects with AD Following 2 IV Infusions 4 Weeks Apart

PK Parameter	Dose 1 (Day 1)		Dose 2 (Day 29)	
	n	Geometric Mean (% CV Geometric Mean)	n	Geometric Mean (% CV Geometric Mean)
C_{max}, µg/mL	45	303 (29)	33	352 (29)
T_{max}, h[a]	45	1.5 (1.0-333.6)	33	2.0 (1.0-4.1)
$AUC_{0\text{-}tau}$, µg·h/mL	40	57217 (26)	32	69670 (29)
C_{trough}, µg·h/mL	33	29.9 (39)	25	34.5 (51)
CL, L/h	32	NC	32	0.008 (45)
V_Z, L	31	NC	31	3.6 (32)
$t_{1/2}$, h	31	NC	31	302 (32)

[a] T_{max} data are presented as median (min-max).
AD, atopic dermatitis; $AUC_{0\text{-}tau}$, area under the serum concentration-time curve over the dosing interval; CL, clearance; C_{max}, maximum concentration; C_{trough}, trough serum concentration; CV, coefficient of variation; h, hours; IV, intravenous; NC, not calculable; PK, pharmacokinetic; $t_{½}$, terminal elimination half-life; T_{max}, time to C_{max}; V_z, volume of distribution based on the terminal elimination phase.

Figure 3. GBR 830 Geometric Mean Serum Concentration-Time Profile in Subjects with AD



Serum concentration was quantified using a validated ELISA method (lower limit of quantitation: 3900 ng/mL).
AD, atopic dermatitis; h, hours; IV, intravenous.

- Low incidence of ADA was observed with no discernible effect on PK or safety (**Table 6**); 6 of 46 GBR 830-treated AD subjects were ADA positive
- GBR 830 was well tolerated; TEAEs occurred with similar incidence between treatment groups and most were mild or moderate in intensity

Table 6. Anti-Drug Antibody Results in Subjects with AD Treated with GBR 830 or Placebo

n (%)[a]	GBR 830 10 mg/kg IV (n=46)	Placebo (n=16)
Negative	40 (87)	15 (94)
Positive	6 (13)	1 (7)[b]

[a] For positive ADA status, results of the confirmatory assay were counted.
[b] Subject showed positive ADA response post-dose and also at baseline with no increase in antibody titers post-dose; lack of immune boosted response indicate that this may be cross reacting antibody.
AD, atopic dermatitis; ADA, anti-drug antibody; IV, intravenous.

CONCLUSION

- GBR 830 was well tolerated and showed a similar PK profile in healthy volunteers and subjects with atopic dermatitis. A favorable linear PK profile with a long half-life, high bioavailability, and no evidence of target-mediated disposition was observed. Anti-drug antibody generation had no discernible effect on PK or safety