A Randomized Phase I Study Comparing Pharmacokinetics, Safety, and Immunogenicity of a High-Concentration Formulation (100 mg/mL) with GP2017 (adalimumab-adaz) Formulation (50 mg/mL), an Adalimumab Biosimilar, in Healthy Male Subjects

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INTRODUCTION

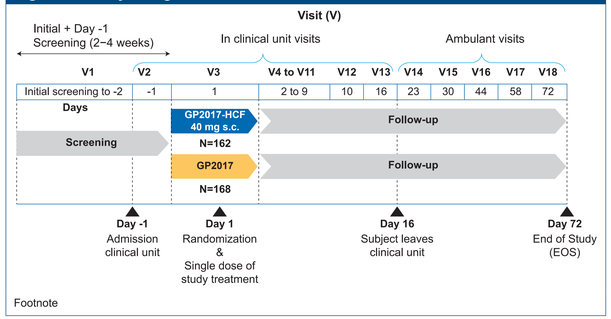
- GP2017 (adalimumab-adaz) is an approved biosimilar of adalimumab (ADL)[1], with a concentration of 50 mg/mL
- Phase 3 studies of GP2017 have demonstrated similar efficacy, safety, and immunogenicity to its reference medicine[2,3]
- High-concentration formulation of GP2017 (GP2017-HCF, with drug concentration 100 mg/mL) was developed to reduce the injection volume, and consequently decrease the number of injections required for patients who need to administer a higher dose
- Apart from the absence of citric acid and sodium chloride in GP2017-HCF, both study formulations are composed of the same compounds including the active ingredient, adalimumab-adaz, and are dispensed in identical devices (prefilled syringes)
- A Phase I study in healthy male subjects was conducted to demonstrate pharmacokinetics (PK) comparability between a newly developed GP2017 citrate-free HCF and the currently approved GP2017

METHODS

Study design and subjects

- This was a multicenter, randomized, double-blind, parallel, two-arm, single-dose study
- Healthy adult male subjects aged 18–55 years were randomized to receive a single 40 mg subcutaneous injection of either GP2017 (50 mg/mL) or GP2017-HCF (100 mg/mL) (**Figure 1**)
- PK, safety, and immunogenicity were assessed over 72 days post-injection

Figure 1. Study design



Footnote

Endpoints and Assessments

- **Primary endpoints**
  - maximum serum concentration (C_{max})
  - area under the concentration–time curve from time zero to infinity (AUC_{0-inf})
  - area under the concentration–time curve from time zero to 360 hours post-dose (AUC_{0-360})
- **Secondary endpoints**

  PK secondary endpoints
  - area under the concentration–time curve from time zero to the last quantifiable concentration (AUC_{0-last})

  Other secondary endpoints
  - immunogenicity: anti-drug antibody formation before and after the drug administration
  - safety assessment: adverse events (AEs), and serious AEs (SAEs)
- PK comparability was concluded when the 90% confidence intervals (CIs) of the ratios of geometric means were within the predefined comparability margin of 0.80 to 1.25

RESULTS

- A total of 331 subjects were randomized, of which 330 received study treatment (162 GP2017-HCF; 168 GP2017)
- Demographics and baseline characteristics were well balanced and comparable between the two treatment groups (**Table 1**)

Table 1. Demographics and baseline characteristics of subjects

Characteristics	GP2017-HCF N=162	GP2017 N=168
Age (years), mean (SD)	36.8 (9.04)	37.8 (9.52)
Male, n (%)	162 (100)	168 (100)
Race, n (%)		
American Indian or Alaska Native	0 (0.0)	1 (0.6)
Asian	1 (0.6)	1 (0.6)
Black or African American	38 (23.5)	26 (15.5)
Multiple	1 (0.6)	0 (0.0)
White	122 (75.3)	140 (83.3)
Ethnicity, n (%)		
Hispanic or Latino	134 (82.7)	140 (83.3)
Not Hispanic or Latino	28 (17.3)	28 (16.7)
Height (cm), mean (SD)	173.7 (6.47)	174.4 (6.65)
Weight (kg), mean (SD)	81.21 (9.10)	81.24 (8.79)
Weight stratification factor, n (%)		
65.0 – <76.0 kg	50 (30.9)	50 (29.8)
76.0 – <92.0 kg	94 (58.0)	100 (59.5)
92.0 – 110.0 kg	18 (11.1)	18 (10.7)
BMI (kg/m^2), mean (SD)	26.90 (2.24)	26.70 (2.34)

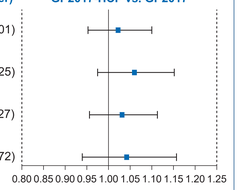
BMI, body mass index; N, total number of subjects treated; n, number of subjects assessed; SD, standard deviation

Pharmacokinetics analysis

- The 90% CIs of the geometric mean ratios (GP2017-HCF/GP2017) for the PK endpoints (C_{max}, AUC_{0-inf}, AUC_{0-360} and AUC_{0-last}) were all contained within the pre-defined comparability margin of 0.80 to 1.25 (**Figure 2**)

Figure 2. Forest plot to compare primary and secondary PK endpoints between the treatment groups

Parameter (unit)	n	Geometric test	LS means reference	Point estimate	Ratio Test/Reference 90% CI (Lower, Upper)
Cmax (ng/mL)	300	3247	3170	1.0242	(0.9536, 1.1001)
AUC0-inf (h*ng/mL)	285	2334410	2201267	1.0605	(0.9758, 1.1525)
AUC0-360 (h*ng/mL)	300	904669	876775	1.0318	(0.9568, 1.1127)
AUC0-last (h*ng/mL)	300	1859656	1782651	1.0432	(0.9404, 1.1572)



CI, confidence interval; LS, least squares; n, number of subjects who received study treatment, completed the study without major protocol deviation and had evaluable PK parameter data. Analysis of variance model performed for PK parameter including treatment as fixed effect and baseline body weight (at Day 1) as covariate

Immunogenicity

- The proportions of subjects with positive ADA and with neutralizing antibodies (NAb) were comparable overall and at all individual visits (**Table 2**)

Table 2. Summary of immunogenicity results

Visit	Result	GP2017-HCF N=162 n (%)	GP2017 N=168 n (%)
Day 1 (Pre-dose)	ADA Positive	1 (0.6)	0
	NAb Positive	1 (0.6)	0
Day 3	ADA Positive	0	0
	NAb Positive	0	0
Day 7	ADA Positive	2 (1.2)	4 (2.4)
	NAb Positive	2 (1.2)	4 (2.4)
Day 10	ADA Positive	2 (1.2)	5 (3.0)
	NAb Positive	2 (1.2)	4 (2.4)
Day 16	ADA Positive	58 (35.8)	50 (29.8)
	NAb Positive	26 (16.0)	24 (14.3)
Day 23	ADA Positive	68 (42.0)	61 (36.3)
	NAb Positive	34 (21.0)	40 (23.8)
Day 30	ADA Positive	43 (26.5)	47 (28.0)
	NAb Positive	29 (17.9)	36 (21.4)
Day 44	ADA Positive	41 (25.3)	44 (26.2)
	NAb Positive	40 (24.7)	44 (26.2)
Day 58	ADA Positive	68 (42.0)	72 (42.9)
	NAb Positive	67 (41.4)	72 (42.9)
Day 72	ADA Positive	94 (58.0)	90 (53.6)
	NAb Positive	93 (57.4)	90 (53.6)
Overall (up to Day 72)	ADA Positive	112 (69.1)	109 (64.9)
	ADA Negative	49 (30.2)	59 (35.1)
	NAb Positive	102 (63.0)	103 (61.3)
	Transient	18 (11.1)	17 (10.1)

The number of subjects of each category at each visit (n) is displayed in the table. Percentage is calculated as 100*n/N. "Overall" indicates a subject had an ADA negative test result at baseline and had at least 1 ADA positive result (ADA-positive) or consistently negative results (ADA-negative) post-baseline. "Transient" indicates that a subject experienced a final negative ADA result at any visit following a positive ADA result.
ADA, anti-drug antibody; NAb, neutralizing antibody; N, total number of subjects treated

Safety

- Single dose administrations of GP2017-HCF and GP2017 were safe and well tolerated
- The overall proportion of subjects with treatment-emergent AEs was comparable between the two groups (**Table 3**)

Table 3. TEAES by primary system organ class (at least 2% of subjects in any treatment group)

Primary system organ class	GP2017-HCF N=162 n (%)	GP2017 N=168 n (%)
Number of subjects with at least 1 event	80 (49.4)	95 (56.5)
General disorders and administration site conditions	55 (34.0)	69 (41.1)
Investigations	16 (9.9)	24 (14.3)
Musculoskeletal and connective tissue disorders	8 (4.9)	14 (8.3)
Nervous system disorders	8 (4.9)	6 (3.6)
Skin and subcutaneous tissue disorders	10 (6.2)	4 (2.4)
Gastrointestinal disorders	8 (4.9)	3 (1.8)
Respiratory, thoracic, and mediastinal disorders	2 (1.2)	6 (3.6)
Eye disorders	1 (0.6)	4 (2.4)
Injury, poisoning, and procedural complications	4 (2.5)	1 (0.6)

TEAEs are events that started or worsened after study treatment.
A subject with multiple occurrences of an event within the same primary system organ class was counted only once.
N, total number of subjects treated; SOC, system organ class; TEAEs, treatment-emergent adverse events

CONCLUSIONS

- The PK comparability between GP2017-HCF and GP2017 demonstrated equal bioavailability of the two formulations, thereby supporting the development of the new formulation of GP2017
- Safety and immunogenicity profiles were comparable between treatment groups and consistent with previously reported adalimumab data

References

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