Assessment of Comparative Immunogenicity in Biosimilar Development: Immunogenicity and Pharmacokinetics Following a Single Dose of M923, a Proposed Biosimilar for Reference Adalimumab (HUMIRA®), Compared with US- and EU-Sourced Reference Adalimumab in Healthy Subjects

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Abstract #605

BACKGROUND

M923 (BAX923), which is being jointly developed by Momenta and Baxalta (now part of Shire), is a proposed biosimilar of reference adalimumab. Reference adalimumab is recognized to elicit anti-drug antibodies (ADAs; seroconversion) in a significant proportion of patients, with a potential negative impact on efficacy. Host factors, including nature of the disease and background immunosuppressive therapy, are associated with the frequency of seroconversion. Normal healthy volunteers provide a relatively homogeneous and sensitive population in which to assess the relative immunogenicity of M923 and reference adalimumab.

OBJECTIVES

- To evaluate pharmacokinetic (PK) bioequivalence between M923 and US-sourced Humira (US Humira), between M923 and EU-sourced Humira (EU Humira), and between US- and EU-sourced Humira.
- To evaluate the safety, tolerability, and immunogenicity of M923, US Humira, and EU Humira in healthy subjects.

METHODS

Study Design

- Phase 1, randomized, double-blind, 3-arm, parallel-group, single-dose study.
- A total of 324 healthy subjects aged 18-55 years were randomized 1:1:1 (~108 per treatment arm).
- A single 40-mg dose of either M923, US Humira, or EU Humira was administered by subcutaneous (SC) injection.
- Conducted at three study sites in the United Kingdom.

Outpatient visit	Residential treatment period			Outpatient visits	
Visit 1	Visit 2			Visits 3 to 10	Visit 11
Days – 45 to – 2	Day -1	Day 1	Days 2-8[a]	Days 9, 11, 15, 22, 29, 36, 43, and 57	Day 71
Screening	Admission/ leligibility checks	SC injection[a] of treatment; PK/safety assessments	Serial PK and safety assessments	PK and safety assessments	Follow-up[c]

PD = pharmacodynamic(s); PK = pharmacokinetic(s); SC = subcutaneous.

[a]Subjects were randomized to one of 3 treatments: M923, EU Humira, or US Humira; [b]Subjects could be discharged from the clinical unit on Day 5, at the discretion of the investigator; [c]Includes safety/tolerability/PK/immunogenicity/exploratory PD assessments.

PK Analysis

- The PK analysis set included all evaluable subjects with sufficient data to calculate at least one primary PK endpoint: maximum observed concentration (C_{max}), area under the serum concentration time curve (AUC) from time zero (pre dose) extrapolated to infinity (AUC_{0-inf}), or AUC from time zero (pre dose) to 336 hours (AUC_{0-336}).
- PK equivalence across the three treatment arms was established if the 90% confidence intervals (CI) for the least squares geometric means of the primary PK parameters for each comparison (M923 vs US Humira, M923 vs EU Humira, US Humira vs EU Humira) fell within the limits of 80.00 to 125.00%, inclusive.

METHODS (CONTINUED)

Anti-Drug Antibodies (ADA) Assessment and Analysis

- Each subject was screened for ADAs against EU Humira and excluded from randomization if positive.
- Following study drug administration, samples were collected over time and screened for antibodies against M923. Positive samples underwent confirmatory assays against M923, US Humira, and EU Humira. Positivity on any confirmatory assay was considered as an overall positive response.
- Confirmed positive samples were assessed to determine titer of ADA, neutralizing potential, and isotype.

Safety Analysis

- Descriptive summaries of vital signs, adverse events (AEs), clinical laboratory tests, electrocardiograms (ECGs), and concomitant medications were provided.

RESULTS

Randomization, Baseline Characteristics, and Demographics

- A total of 324 subjects were enrolled: 109 in M923 arm; 108 in US Humira arm; 107 in EU Humira arm.
- All subjects receiving study medication were followed for 71 days; there were no premature withdrawals or discontinuations.
- Demographic and baseline characteristics, including age, weight, height, BMI, sex, and race were similar across treatment arms **(Table 1)**.

Table 1: Demographics and Baseline Characteristics

Parameter	Statistic	M923 N=109	US Humira N=108	EU Humira N=107
Age (years)	Mean	32.2	32.9	32.1
	Min, Max	18, 51	18, 53	18, 54
Weight (kg)	Mean	79.00	78.54	77.85
	Min, Max	61.7, 99.2	60.1, 98.7	61.7, 99.0
Height (cm)	Mean	176.50	177.44	176.48
	Min, Max	153.0, 194.0	161.0, 202.0	152.0, 194.0
BMI (kg/m²)	Mean	25.36	24.92	24.99
	Minimum	19.65, 29.67	19.16, 29.87	19.78, 29.89
Sex, n (%)	Male	106 (97.2%)	106 (98.1%)	103 (96.3%)
	Female	3 (2.8%)	2 (1.9%)	4 (3.7%)
Race, n (%)	White	89 (81.7%)	93 (86.1%)	93 (86.9%)
	Black	7 (6.4%)	8 (7.4%)	6 (5.6%)
	Asian	5 (4.6%)	4 (3.7%)	4 (3.7%)
	Other	8 (7.3%)	3 (2.8%)	4 (3.7%)

RESULTS (CONTINUED)

Pharmacokinetics

- Nine of 324 subjects who received study drug were excluded from the PK analysis set: 5 failed to receive a complete dose; 4 had quantifiable pre-dose concentrations greater than 5% of C_{max}.
- 315 subjects were included in the PK analysis (107 on M923, 105 on US Humira, and 103 on EU Humira).
- Following administration of a single dose, PK profiles of M923, US Humira, and EU Humira were highly similar **(Figure 1)**. Pre-specified criteria for success were met for all comparisons **(Table 2)**.

Figure 1: Mean Serum Concentration-time Profiles

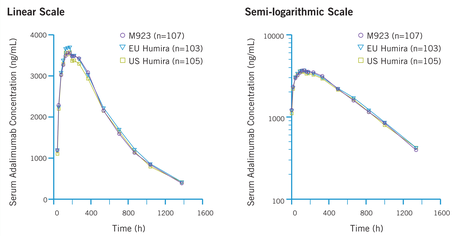

Table 2: Statistical Comparison of Primary PK Parameters

Parameter (unit)	Treatment	n	Geometric LS Mean	95% CI	Treatment Comparison		
					Pair	Ratio (%)	90% CI
C_{max} (ng/mL)	M923	107	3907	(3738, 4084)	M923/ EU Humira	99.39	(94.25, 104.81)
	EU Humira	103	3931	(3758, 4113)	M923/ US Humira	102.58	(97.31, 108.14)
	US Humira	105	3809	(3643, 3983)	—	—	—
AUC_{0-inf} (ng*h/mL)	M923	101	2641000	(2479000, 2813000)	M923/ EU Humira	100.90	(93.48, 108.90)
	EU Humira	95	2617000	(2452000, 2794000)	M923/ US Humira	104.20	(96.47, 112.54)
	US Humira	91	2534000	(2371000, 2709000)	—	—	—
AUC_{0-336} (ng*h/mL)	M923	106	1053000	(1010000, 1098000)	M923/ EU Humira	100.51	(95.55, 105.73)
	EU Humira	100	1048000	(1003000, 1094000)	M923/ US Humira	102.94	(97.88, 108.27)
	US Humira	101	1023000	(979700, 1068000)	—	—	—

Anti-Drug Antibodies (ADA) Assessment and Analysis

- The incidences of ADAs and nADAs were comparable across the 3 treatment arms **(Table 3)**.
  - A similar incidence of confirmed positive ADA response by study day was observed for each confirmation assay (M923, US Humira, EU Humira) across study arms.
  - Higher titers were recorded for 1 subject on M923, 2 subjects on US Humira, and 1 subject on EU Humira; all were associated with detectable neutralizing anti-drug antibodies (nADAs).
- The majority of ADAs were IgG. Eleven subjects had confirmed IgE ADA: 1 on M923, 7 on US Humira, and 3 on EU Humira. Seven of 11 IgE were associated with nADA (5 on US Humira and 2 on EU Humira). Clinical correlates of IgE were not reported.
- The mean time to first seroconversion was comparable across the 3 arms **(Table 4)**.
- Incidence of ADAs and nADAs for each study visit were also comparable across treatments.
- Seroconversion was common. Most ADAs were non-neutralizing.
- Irrespective of treatment, there was a trend of lower overall exposure (AUC) and $t_{1/2}$ and higher CL/F in the presence of ADAs compared to absence of ADAs, and in the presence of nADAs compared to absence of nADAs. There was also a trend for lower exposure with nADAs compared with ADAs, although the analysis is limited by small sample sizes.

Table 3: Incidence of ADAs and nADAs, and Time to Seroconversion, by Treatment

Assessment	M923 (N=109)	US Humira (N=108)	EU Humira (N=107)
Confirmed positive ADA status	85 (78.0%)	87 (80.6%)	84 (78.5%)
Confirmed positive nADA status	18 (16.5%)	30 (27.8%)	22 (20.6%)
Mean time (day) to seroconversion	45.4	42.4	44.9

Table 4: Incidence of ADA and nADA formation by Study Day and Treatment

Study Day/ Time Point, n (%)	Overall Positive Confirmed ADA Response			Neutralizing ADA Positive Response		
	M923 N=109	EU Humira N=107	US Humira N=108	M923 N=109	EU Humira N=107	US Humira N=108
Day 1/ Pre dose	0 (0.0%)	1 (0.9%)	3 (2.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Day 8/ 168 hours	3 (2.8%)	6 (5.6%)	7 (6.5%)	1 (0.9%)	1 (0.9%)	2 (1.9%)
Day 15/ 336 hours	16 (14.7%)	17 (15.9%)	19 (17.6%)	0 (0.0%)	2 (1.9%)	3 (2.8%)
Day 29/ 672 hours	20 (18.3%)	20 (18.7%)	26 (24.1%)	3 (2.8%)	3 (2.8%)	9 (8.3%)
Day 43/ 1008 hours	33 (30.3%)	32 (29.9%)	41 (38.0%)	6 (5.5%)	7 (6.5%)	10 (9.3%)
Day 57/ 1344 hours	63 (57.8%)	61 (57.0%)	65 (60.2%)	11 (10.1%)	15 (14.0%)	18 (16.7%)
Day 71/ Follow-up	85 (78.0%)	81 (75.7%)	79 (73.1%)	16 (14.7%)	17 (15.9%)	25 (23.1%)
Overall status	85 (78.0%)	84 (78.5%)	87 (80.6%)	18 (16.5%)	22 (20.6%)	30 (27.8%)

Safety

- The incidence, severity, and type of AEs were similar across study arms.
- There were no deaths and no AEs leading to early withdrawal.
- One subject in the EU Humira arm reported 3 serious but unrelated AEs: foot fracture, laceration, and wound infection.
- AEs of special interest included:
  - System Organ Class 'Infections and Infestations' were reported by 14 subjects on M923, 16 subjects on US Humira, and 20 subjects on EU Humira.
  - AEs related to injection site reactions were reported by 11 subjects on M923, 9 subjects on US Humira, and 5 subjects on EU Humira. Most were assessed as mild and related to study treatment.
- No meaningful differences over time across the treatment arms were observed in any safety assessments: laboratory, ECG, or vital signs (data not shown).

Table 5: Summary of Safety Results

Adverse Event Type	M923 N=109 n (%)	US Humira N=108 n (%)	EU Humira N=107 n (%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious AEs	0 (0.0%)	0 (0.0%)	1 (0.9%)
AEs leading to early withdrawal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any AEs	52 (47.7%)	55 (50.9%)	57 (53.3%)
Treatment-related AEs (Possible or Probable)	36 (33.0%)	32 (29.6%)	28 (26.2%)

DISCUSSION/CONCLUSIONS

- M923 was shown to be bioequivalent on all of the primary endpoints:
  - C_{max} ratio of M923 to EU Humira was 99.39 (90% CI 94.25-104.81) and to US Humira was 102.58 (90% CI 97.31 to 108.14).
  - AUC_{0-inf} ratios of M923 to EU Humira was 100.90 (90% CI 93.48-108.90) and to US Humira was 104.20 (90% CI 96.47-112.54).
- The majority of subjects had seroconverted by Day 71. The rate of seroconversion over time was similar to that reported by Kauer et al[1] (a study in healthy subjects comparing adalimumab biosimilar with US- and EU-sourced Humira: 53.7-67.2% through Day 63, compared with 57.0-60.2% through Day 57 in the present study).
- The occurrence of nADAs was similar across treatment arms.
- A comparable safety profile was observed across study arms.
- These results support the further development of M923, including the ongoing M923 pivotal clinical trial in patients with chronic plaque psoriasis.

REFERENCES

1. Kaur P, et al. Ann Rheum Dis 2016;0:1–8.

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