Supplemental digital content

Inclusion/exclusion criteria VOLTAIRE®-AI

Healthy male subjects were eligible for participation in the trial if they fulfilled the following inclusion criteria:
1. Healthy male, non-athletic (≤1 hour of exercise per week), Caucasian subjects according to the Investigator's assessment, based on a complete medical history including a physical examination, vital signs (blood pressure [BP], pulse rate [PR]), 12-lead electrocardiogram [ECG], and clinical laboratory tests.
2. Aged between 18 and 65 years (inclusive)
3. Body mass index [BMI] of 18.0 to 30.0 kg/m^2 (inclusive)
   - BMI 18.0 to <20.0 kg/m2, or
   - BMI 20.0 to <25.0 kg/m2, or
   - BMI 25.0 to ≤30.0 kg/m2
4. Signed and dated written informed consent prior to admission to the trial in accordance with good clinical practice [GCP] and local legislation.
5. Subjects agreed to use an acceptable method of contraception during the trial and for 6 months after the administration of trial medication.

Subjects were not eligible for participation in the trial if they met any of the following exclusion criteria:
1. Any finding in the medical examination (including BP, PR, or ECG) that deviated from the norm and was judged as clinically relevant by the Investigator
2. Any evidence of a concomitant disease judged as clinically relevant by the Investigator, including gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, hormonal disorders, or diseases of the central nervous system (including, but not limited to, any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
3. History of relevant orthostatic hypotension, fainting spells, or blackouts
4. Chronic or relevant acute infections
5. Positive result for human immunodeficiency virus, hepatitis B, or hepatitis C at screening
6. History of relevant allergy or hypersensitivity including allergy to the trial medication, its excipients or device materials (e.g. natural rubber or latex)
7. Intake of drugs with a long $t_{1/2}$ (more than 24 hours) within 30 days or less than 5 half-lives of the respective drug prior to administration of trial medication
8. Within 10 days prior to administration of trial medication, use of drugs that might have reasonably influenced the results of the trial
9. Previous exposure to a biologic drug
10. Intake of an investigational drug in another trial within 2 months prior to intake of trial medication in this trial or intake of an investigational drug during the course of this trial
11. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
12. Inability to refrain from smoking during days of confinement at the trial site
13. Alcohol abuse (consumption of more than 4 units/day)
14. Unwillingness/inability to refrain from intake of alcoholic beverages from 48 hours prior to the trial medication administration and until day 14 post trial medication administration; and to limit alcohol intake to a maximum of 3 units per day until the end of trial
15. Drug abuse or positive drug screening

16. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
17. Intention to perform excessive physical activities within 1 week prior to administration of trial medication or contact sport during the entire trial and unwilling to avoid vigorous exercise for 14 days post-dosing
18. Inability to comply with dietary regimen of trial site
19. Any out-of-range laboratory values considered clinically significant by the Investigator; subjects with creatine kinase values 2 times the upper limit of normal at day -1 were excluded from participation
20. Subject was assessed as unsuitable for inclusion by the Investigator, for instance, because he was considered not able to understand and comply with trial requirements, or had a condition that would not allow safe participation in the trial
21. Subjects with any immunological disorders or auto-immune disorders (e.g. rheumatoid arthritis, lupus erythematosus, scleroderma, etc.)
22. Subject who received a live vaccine within 12 weeks prior to enrolling in the trial
23. History of tuberculosis or positive finding in interferon-gamma release assay (IGRA)
24. Evidence of skin irritation or infection at the planned injection site

Healthy male or female subjects were eligible for participation in the trial if they fulfilled the following inclusion criteria:
1. Aged between 18 and 65 years (inclusive)
2. BMI of >17.5 to <35.0 kg/m^2
3. Healthy male or female subjects, according to the Investigator's assessment, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
4. Subjects who meet any of the following criteria:
    - Surgically sterilized (confirmed 6 months prior to enrollment)
    - Have surgically sterilized sexual partner (confirmed 6 months prior to enrollment)
    - Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of follicle-stimulating hormone above 40 U/L and estradiol below 30 ng/L is confirmatory)
5. Subjects who agree to use an adequate contraception, starting from the beginning of the trial and until 6 months after the dose of trial drug (e.g. any of the following methods plus condom: implants, injectables, combined oral or vaginal contraceptives, intrauterine device)
6. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial

Subjects were not eligible for participation in the trial if they met any of the following exclusion criteria:
1. Previous exposure to adalimumab or proposed adalimumab biosimilar drugs
2. Any finding in the medical examination (including BP, PR, or ECG) that deviated from normal and was judged as clinically relevant by the Investigator
3. Any evidence of a concomitant disease judged as clinically relevant by the Investigator including gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, hormonal

disorders or diseases of the central nervous system (including, but not limited to, any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
4. History of relevant orthostatic hypotension, fainting spells, or blackouts
5. Chronic or relevant acute infections
6. Positive result for HIV, hepatitis B, or hepatitis C at screening
7. History of relevant allergy or hypersensitivity including allergy to the trial medication, its excipients or device materials (e.g. natural rubber or latex)
8. Within 10 days prior to administration of trial medication, use of drugs that might have reasonably influenced the results of the trial
9. Intake of an investigational drug in another trial within 2 months or 5 half-lives (whichever is longer) prior to planned administration of the trial medication in this trial or intake of an investigational drug during the course of this trial
10. Alcohol abuse (consumption of more than 4 units/day)
11. Unwillingness/inability to refrain from intake of alcoholic beverages from 48 hours prior to the trial medication administration and until day 14 post trial medication administration; and to limit alcohol intake to a maximum of 3 units per day until the end of trial
12. Drug abuse or positive drug screening
13. Blood donation of more than 500 mL within 30 days prior to administration of trial medication or intended donation during the trial
14. Intention to perform excessive physical activities within 4 days prior to administration of trial medication or contact sport during the entire trial and unwilling to avoid vigorous exercise for 14 days post dosing
15. Inability to comply with dietary regimen of trial site
16. Any out-of-range laboratory values considered clinically significant by the Investigator; subjects with creatine kinase values 2 times the upper limit of normal at day -1 were excluded from participation
17. Subject was assessed as unsuitable for inclusion by the Investigator, for instance, because he/she was considered not able to understand and comply with trial requirements, or had a condition that would not allow safe participation in the trial
18. Subjects with any immunological disorders or auto-immune disorders (e.g. rheumatoid arthritis, lupus erythematosus, scleroderma, etc.)
19. Subject who received a live vaccine within 12 weeks prior to enrolling in the trial
20. History of tuberculosis or positive finding in IGRAs
21. Evidence of skin irritation or infection at the planned injection site
22. Currently enrolled in another investigational device or drug study
23. Any condition that, in the Investigator's opinion, makes them an unreliable study subject or unlikely to complete the trial
24. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

<u>AI and PFS injection process</u>

The autoinjector (AI) contains a pre-filled syringe (PFS) and is preassembled for immediate use. After letting the AI warm up to ambient temperature, washing hands, and disinfecting the skin, the user removes the cap and firmly presses the AI against the appropriate raised skin location at a 90 degree angle. The injection is started by pushing the injection button, which is confirmed by a "click" sound. The AI is held firmly against the skin for 10 seconds to deliver the entire dose and its completion is

confirmed by inspecting the plunger through the window. As the AI is removed from the skin a needle guard automatically covers the needle for protection.

The standard PFS is a single-use syringe with a winged grip to ease injection. After letting the PFS warm up to ambient temperature, washing hands, and disinfecting the skin, the user removes the cap and inserts the needle at a 45 degree angle into the appropriate raised skin location. The plunger is pushed to the bottom of the syringe to deliver the entire dose, then the needle is removed from the skin.

PK parameters by BMI group category in VOLTAIRE®-AI

		AI			PFS	
Parameter	**N**	**gMean**	**gCV (%)**	**N**	**gMean**	**gCV (%)**
Low BMI (18.0 to <20.0 kg/m^2)						
$AUC_{0-\infty}$[a] (µg·h/mL)	5	2360	24.5	6	4010	44.6
$\%AUC_{tz-\infty}$ (%)	5	2.23	1030	6	22.4	51.4
AUC_{0-1032} (µg·h/mL)	5	2150	14.3	6	3010	29.1
$AUC_{0-1032,W,norm}$ (µg·h/mL/kg)	5	32.1	13.6	6	48.6	40.0
C_{max} (µg/mL)	5	4.83	11.6	6	5.82	43.7
$C_{max,W,norm}$ (µg/mL/kg)	5	0.0721	11.9	6	0.0941	55.0
t_{max}[b] (h)	5	108	60.0; 169	6	132	8.00; 168
$t_{1/2}$ (h)	5	155	115	6	479	50.0
Medium BMI (20.0 to <25.0 kg/m^2)						
$AUC_{0-\infty}$[a] (µg·h/mL)	15	2240	51.1	15	2210	40.9
$\%AUC_{tz-\infty}$ (%)	15	9.08	200	15	4.69	352
AUC_{0-1032} (µg·h/mL)	15	1970	39.7	15	1990	32.1
$AUC_{0-1032,W,norm}$ (µg·h/mL/kg)	15	26.3	40.6	15	26.2	35.4
C_{max} (µg/mL)	15	4.01	29.2	15	3.85	26.0
$C_{max,W,norm}$ (µg/mL/kg)	15	0.0535	33.4	15	0.0505	28.4
t_{max}[b] (h)	15	108	48.0; 132	15	120	24.0; 336
$t_{1/2}$ (h)	15	243	64.5	15	208	76.4
High BMI (25.0 to ≤30.0 kg/m^2)						
$AUC_{0-\infty}$[a] (µg·h/mL)	15	1840	73.5	14[c]	1520	48.8
$\%AUC_{tz-\infty}$ (%)	15	5.73	485	14[c]	5.03	280
AUC_{0-1032} (µg·h/mL)	15	1580	59.6	14[c]	1370	43.7
$AUC_{0-1032,W,norm}$ (µg·h/mL/kg)	15	18.6	59.0	14[c]	15.6	47.1
C_{max} (µg/mL)	15	3.30	21.5	15	2.55	49.9
$C_{max,W,norm}$ (µg/mL/kg)	15	0.0389	27.5	15	0.0289	57.2
t_{max}[b] (h)	15	132	59.9; 337	15	168	84.0; 336
$t_{1/2}$ (h)	15	189	179	14[c]	177	115

[a]Based on observed last concentration values

[b]t_{max} is given as median (minimum; maximum)

[c]Values could not be calculated for one subject, due to the lack of appropriate terminal phase (only one value in the elimination phase not below limit of quantification)

$\%AUC_{tz-\infty}$ the percentage of the area under the concentration-time curve from time tz to infinity obtained by extrapolation, *AI* autoinjector, *$AUC_{0-\infty}$* area under the plasma concentration-time curve from 0 extrapolated to infinity, *$AUC_{0-1,032}$* area under the plasma concentration-time curve from 0 to 1,032 hours post-dose, *$AUC_{0-1032,W,norm}$* $AUC_{0-1,032}$ normalized by weight, *C_{max}* maximum plasma concentration, *$C_{max,W,norm}$* C_{max} normalized by weight, *gCV* geometric coefficient of variation, *gMean* geometric mean, *PFS* prefilled syringe, *$t_{1/2}$* terminal half-life, *t_{max}* time to reach maximum concentration