Supplementary Information

Switching Between Adalimumab Reference Product and BI 695501 in Patients With Chronic Plaque Psoriasis (VOLTAIRE-X): A Randomized Controlled Trial

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Supplemental Materials

1) Eligibility Criteria

2) Supplementary Tables 1 and 2

3) Supplementary Figures 1–3

4) Patient details: TEAE diffuse axonal injury and demyelination

1) Eligibility Criteria

Inclusion Criteria

1. Males and females aged ≥ 18 to < 80 years at screening who had a diagnosis of moderate-to-severe chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of trial drug (a self-reported diagnosis confirmed by the investigator was acceptable), and who had been stable per investigator opinion for the last 2 months with no changes in morphology or significant flares at both screening and baseline, with:

    a. involved body surface area ≥ 10%, and

    b. Psoriasis Area and Severity Index score ≥ 12, and

    c. Static Physician's Global Assessment score of ≥ 3.

2. Participants of reproductive potential (childbearing potential) were required to be willing and able to use highly effective methods of birth control per International Council for Harmonization M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly during the trial and for 6 months following completion or discontinuation from the trial medication.

3. Signed and dated written informed consent in accordance with Good Clinical Practice and local legislation prior to admission to the trial.

4. Patients who were candidates for systemic therapy or phototherapy according to investigator judgement.

Exclusion Criteria

1. Active ongoing inflammatory diseases other than psoriasis that might confound trial evaluations according to investigator's judgement.

2. Prior exposure to any biologic therapies for any autoimmune diseases (including, but not limited to, rheumatoid arthritis, psoriasis, or Crohn's disease).

3. Patients with a significant disease other than psoriasis and/or a significant uncontrolled disease (such as, but not limited to, nervous system, renal, hepatic, endocrine, hematological, autoimmune, or gastrointestinal disorders). A significant disease was defined

as a disease which, in the opinion of the investigator, may (i) put the patient at risk because of participation in the trial, (ii) influence the results of the trial, or (iii) cause concern regarding the patient's ability to participate in the trial.

4. Major surgery (major according to the investigator's assessment) performed within 12 weeks before enrollment or planned within 6 months after screening, e.g. total hip replacement.

5. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated (in the opinion of the Investigator) basal cell carcinoma of the skin or in situ carcinoma of uterine cervix.

6. Patients who must or wished to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial.

7. Currently enrolled in another investigational device or drug trial, or less than 30 days (or less than 5 half-lives, whichever is longer) as ending another investigational device or drug trial(s), or receiving other investigational treatment(s).

8. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, made the patient an unreliable trial subject or unlikely to complete the trial.

9. Women who were pregnant, nursing, or who planned to become pregnant during the course of this trial or within the period at least 6 months following completion or discontinuation from the trial medication.

10. Forms of psoriasis (e.g. pustular, erythrodermic and guttate) other than chronic plaque psoriasis. Drug-induced psoriasis (i.e. new onset or current exacerbation from e.g. beta blockers or lithium).

11. Primary or secondary immunodeficiency (history of, or currently active), including known history of HIV infection or a positive HIV test at screening (per the investigator discretion and where mandated by local authorities).

12. Known chronic or relevant acute tuberculosis (TB); interferon-gamma release assays TB test or purified protein derivative skin test were to be performed according to the labeling for adalimumab reference product. If the result was positive, patients may participate in the trial if further work-up (according to local practice/guidelines) established conclusively that

the patient had no evidence of active TB. If latent TB was confirmed, then treatment must have been initiated before treatment in the study and continued according to local country guidelines.

13. Known clinically significant (per investigator opinion) coronary artery disease, significant cardiac arrhythmias, moderate-to-severe congestive heart failure (New York Heart Association Classes III or IV), or interstitial lung disease observed on chest x-ray.

14. Patients with a history of any clinically significant adverse reaction (including serious allergic reactions, or anaphylactic reaction, or hypersensitivity) to murine or chimeric proteins, previously used biological drug or its excipients, or natural rubber and latex.

15. Positive serology for hepatitis B virus or hepatitis C virus.

16. Receipt of a live/attenuated vaccine within 12 weeks prior to the screening visit; patients who were expecting to receive any live/attenuated virus or bacterial vaccinations during the trial or up to 3 months after the last dose of trial drug.

17. Any treatment (including biologic therapies) that, in the opinion of the investigator, may place the patient at unacceptable risk during the trial.

18. Known active infection of any kind (excluding fungal infections of nail beds), any major episode of infection requiring hospitalization or treatment with intravenous anti-infectives within 4 weeks of the screening visit or completion of oral anti-infectives within 2 weeks of the screening visit.

19. Aspartate aminotransferase or alanine aminotransferase > 2.5 times upper limit of normal at screening.

20. Hemoglobin < 8.0 g/dL at screening.

21. Platelets < 100,000/µL at screening.

22. Leukocyte count < 4000/µL at screening.

23. Calculated creatinine clearance < 60 mL/min at screening.

Supplemental Table 1. Statistical analysis population

Parameter analyzed	Study population
PK	PK set: All patients who received study treatment and for whom at least one evaluable primary PK parameter was available and who had not been excluded due to a protocol violation relevant to the evaluation of PK.
Efficacy	Per-protocol set: All randomized patients who received at least one dose of study treatment, with all relevant efficacy measures for at least one efficacy endpoint prior to and post-randomization, and no protocol violations.
Immunogenicity	Treated set: All patients treated with at least one dose of study treatment during the randomized phase Run-in treated set: All patients treated with at least one dose of adalimumab RP during the run-in period.
Safety	Treated set: All patients treated with at least one dose of study treatment during the randomized phase Run-in treated set: All patients treated with at least one dose of adalimumab RP during the run-in period.

PK pharmacokinetic.

Supplemental Table 2. TEAEs by system organ class and preferred term occurring in ≥ 2% during the post-randomization period (safety evaluation set[a])

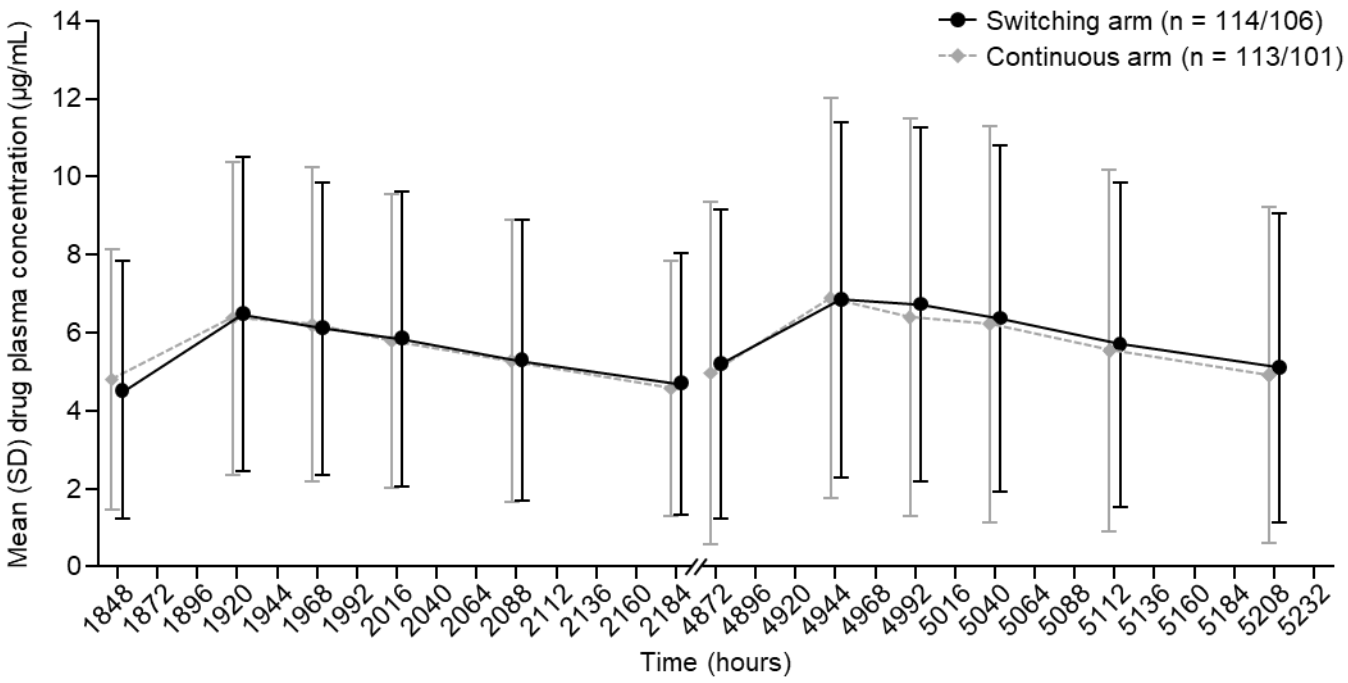
TEAEs, *n* (%)	Switching (*n* = 118)	Continuous (*n* = 120)	Total (*n* = 238)
Infections and infestations	35 (29.7)	29 (24.2)	64 (26.9)
Nasopharyngitis	11 (9.3)	5 (4.2)	16 (6.7)
Respiratory tract infection viral	4 (3.4)	5 (4.2)	9 (3.8)
Rhinitis	5 (4.2)	4 (3.3)	9 (3.8)
Upper respiratory tract infection	3 (2.5)	3 (2.5)	6 (2.5)
Gastrointestinal infection	1 (0.8)	3 (2.5)	4 (1.7)
Pharyngitis	3 (2.5)	0 (0.0)	3 (1.3)
Upper respiratory tract infection bacterial	3 (2.5)	0 (0.0)	3 (1.3)
Metabolism and nutrition disorders	4 (3.4)	4 (3.3)	8 (3.4)
Hypercholesterolemia	0 (0.0)	3 (2.5)	3 (1.3)
Nervous system disorders	9 (7.6)	13 (10.8)	22 (9.2)
Headache	6 (5.1)	6 (5.0)	12 (5.0)
Vascular disorders	3 (2.5)	0 (0.0)	3 (1.3)
Hypertension	3 (2.5)	0 (0.0)	2 (1.3)
Respiratory, thoracic, and mediastinal disorders	2 (1.7)	7 (5.8)	9 (3.8)
Cough	0 (0.0)	3 (2.5)	3 (1.3)
Gastrointestinal disorders	10 (8.5)	10 (8.3)	20 (8.4)
Diarrhea	2 (1.7)	3 (2.5)	5 (2.1)
Skin and subcutaneous tissue disorders	6 (5.1)	6 (5.0)	12 (5.0)

TEAEs, *n* (%)	Switching (*n* = 118)	Continuous (*n* = 120)	Total (*n* = 238)
Psoriasis	3 (2.5)	2 (1.7)	5 (2.1)
Musculoskeletal and connective tissue disorders	11 (9.3)	11 (9.2)	22 (9.2)
Arthralgia	3 (2.5)	4 (3.3)	7 (2.9)
Back pain	1 (0.8)	3 (2.5)	4 (1.7)
General disorders and administration site conditions	5 (4.2)	11 (9.2)	16 (6.7)
Injection-site erythema	3 (2.5)	5 (4.2)	8 (3.4)
Investigations	17 (14.4)	15 (12.5)	32 (13.4)
Weight increased	5 (4.2)	2 (1.7)	7 (2.9)
Blood creatine phosphokinase increased	4 (3.4)	1 (0.8)	5 (2.1)
Mycobacterium tuberculosis complex test positive	3 (2.5)	2 (1.7)	5 (2.1)
Weight decreased	2 (1.7)	3 (2.5)	5 (2.1)

[a]All patients who received at least one dose of study treatment in the randomized phase.

TEAE treatment-emergent adverse event.

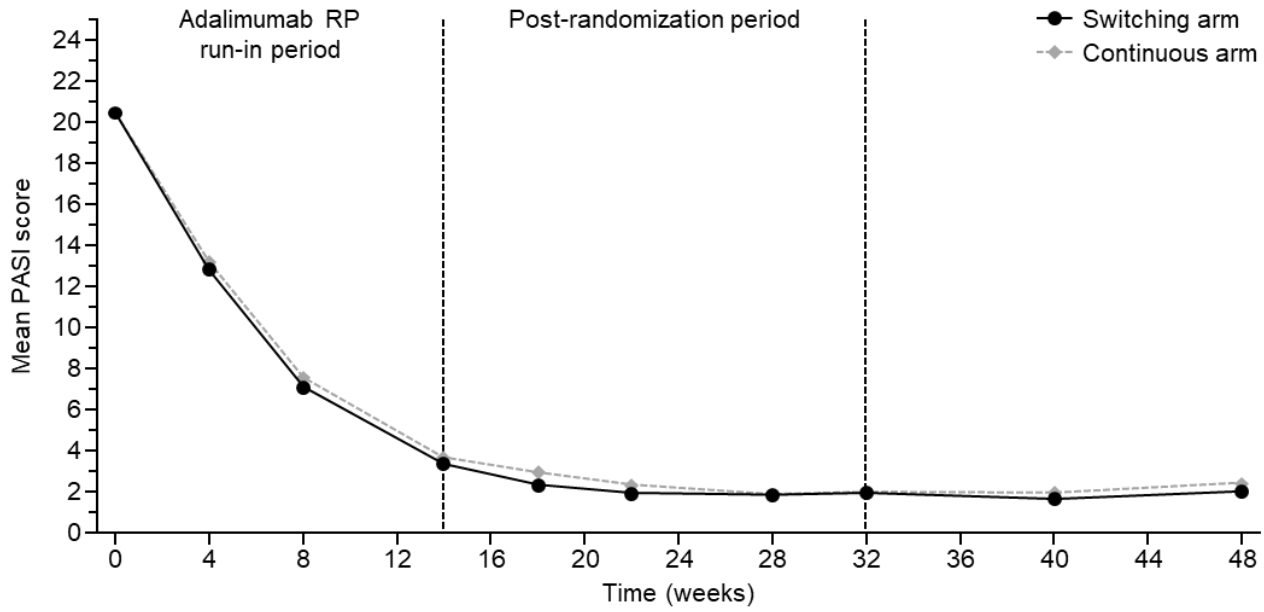
Supplemental Figure 1. Arithmetic Mean Plasma Concentration: Time Profiles from Weeks 12 to 14, and Weeks 30 to 32 for the Switching and Continuous Arms (Pharmacokinetic Set[a])



[a]All patients who received study treatment and for whom at least one primary pharmacokinetic parameter was available.

SD standard deviation.

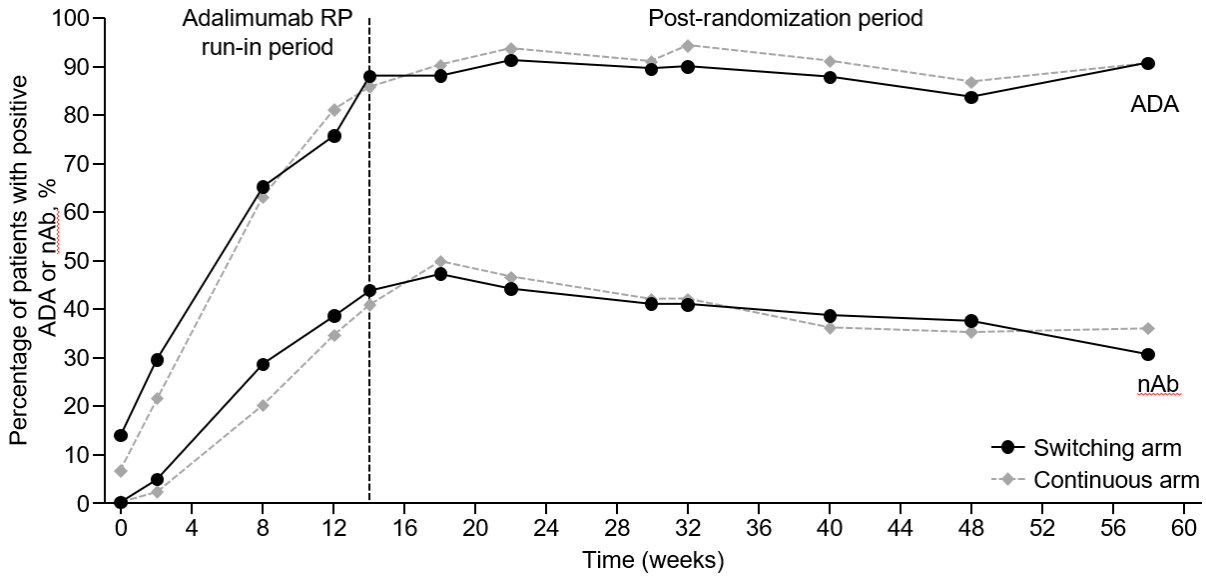
Supplemental Figure 2. Mean PASI score over time in run-in and post-randomization periods (per-protocol set[a])



[a]All patients who were randomized and received at least one dose of study treatment, had all relevant efficacy measures for at least one secondary efficacy endpoint prior to and post-randomization, and had no significant, relevant, or important protocol violations.

PASI Psoriasis Area and Severity Index, *RP* reference product.

Supplemental Figure 3. Proportion of patients with positive ADA and nAb in the run-in and post-randomization periods over time by treatment group (treated set[a])



[a]All patients treated with at least one dose of study treatment during the randomized phase.

ADA antidrug antibodies, *nAb* neutralizing antidrug antibodies.

4) Patient details

A 64-year-old woman who presented with concomitant COPD and hypertension at baseline had her study medication discontinued following an event of diffuse axonal injury and demyelination during the run-in period with adalimumab RP. The patient subsequently died after the end of the trial (cause of death unknown). Although the study investigator considered the events of diffuse axonal injury and demyelination as related to the study drug and the unknown death as not related to the study drug, for regulatory purposes the events of diffuse axonal injury, demyelination, and death were all considered as potentially related to the study drug.