Online Resources

Safety of adalimumab biosimilar MSB11022 (acetate-buffered formulation) in patients with moderately-to-severely active rheumatoid arthritis

Christopher J. Edwards, Joëlle Monnet, Martin Ullmann, Pantelis Vlachos, Veranika Chyrok, Vishal Ghori

Correspondence to: Christopher J. Edwards

cedwards@soton.ac.uk

NIHR Clinical Research Facility, University of Southampton, Southampton, UK

Online Resources Table of Contents

Online Resource 1 List of principal investigators

Site #	Principal investigator	Site name
101	Dr med. Andrea Everding	Hamburger Rheuma Forschungszentrum II MVZ für Rheumatologie und Autoimmunmedizin Hamburg GmbH/ Mönckebergstraße 27, 20095 Hamburg, Germany
102	Dr med. Siegfried Wassenberg	Rheumazentrum Ratingen –Studienambulanz GbR Rosenstraße 2, 40882 Ratingen Germany
112	Dr Tekla Szilassy	Synexus Magyarország Egészségügyi Szolgáltató Kft.- Zalaegerszeg AS, Zárda u. 11. Zalaegerszeg 8900 Hungary
114	Dr Edit Drescher	Vital Medical Center, József Attila u. 17, Veszprém 8200 Hungary
115	Dr Kata Kerekes	Mentaház Magánorvosi Központ, Nagy László u. 1, Székesfehérvár 8000 Hungary
116	Dr Ildikó Rápolthy	DRC Székesfehérvár, Seregélyesi út 17, Székesfehérvár 8000 Hungary
117	Dr Magdolna Nagy	Óbudai Egészségügyi Centrum Kft., Lajos u. 74-76, Budapest 1036 Hungary
119	Dr Annamária Silló	Dr Kenessey Albert Kórház-Rendelőintézet, Rákóczi u. 125-127, Balassagyarmat 2660 Hungary
120	Dr Márta Megyaszai	Revita Reumatológiai Rendelő, Margit krt. 50-52, Budapest 1023 Hungary
126	Dr Rajan Madhok	Glasgow Royal Infirmary, Department of Rheumatology, 84 Castle Street, Glasgow, Strathclyde, G4 0SF, United Kingdom
127	Dr Hasan Tahir	Whipps Cross University Hospital, Department of Rheumatology, Whipps Cross Road, Leytonstone, London, E11 1NR, United Kingdom
128	Prof. Christopher Edwards **Coordinating Investigator**	NIHR Wellcome Trust Clinical Research Facility, Mailpoint 218, Level C, West Wing, University Hospital Southampton, Tremona Road, Southampton, SO16 6YD, United Kingdom
301	Eva Dokoupilova, MD	MEDICAL PLUS s.r.o. Obchodni 1507, 686 01 Uherske Hradiste, Czech Republic
303	Petr Vitek, MD	PV-Medical s.r.o. Stefanikova 477, 760 01 Zlin, Czech Republic
304	Zuzana Urbanova, MD	Revmatologicka ambulance Petra Rezka 1090/3, 140 00 Praha 4, Czech Republic
305	Sylva Brtnikova, MD	CCBR Ostrava, s.r.o. 28. rijna 3348/65, 702 00 Ostrava, Czech Republic
306	Zuzana Stejfova, MD	Revmatologicka ambulance Taborska 325/57, 140 00 Praha 4 Nusle, Czech Republic
307	Dagmar Galatikova, MD	Revmatologie Bruntal, s.r.o. Zahradni 16, 792 01 Bruntal, Czech Republic
308	Lucie Podrazilova, MD, PhD	Revma Praha s.r.o. Seydlerova 2451, 158 00 Praha, Czech Republic
309	Vlasta Gollerova, MD	Clintrial s.r.o. Pocernicka 16, 100 00 Praha 10, Czech Republic
310	Maria Filkova, MD, PhD	Revmatologicky ustav Na Slupi 4, 128 50 Praha 2, Czech Republic
311	Lubos Janu, MD, PhD	A-shine, s.r.o. Smrkova 23, 312 00 Plzen, Czech Republic
401	Magdalena Krajewska-Włodarczyk	ETYKA Ośrodek Badan Klinicznych 1 Maja 13, 10-117 Olsztyn, Poland
402	Sławomir Jeka	NZOZ “Nasz Lekarz”

Site #	Principal investigator	Site name
		Szczytna 20, 87-100 Toruń, Poland
403	Joanna Goździk	Centrum Medyczne Angelius Provita, Fabryczna 13d, 40-611 Katowice, Poland
404	Piotr Wiland	NZOZ Biogenes Sp. z o.o pl. Bzowy 1, 53-224 Wrocław, Poland
405	Mariusz Korkosz	Małopolskie Centrum Medyczne S.C., Rejtana 2, 30-510 Kraków, Poland
406	Iwona Dankewicz-Fares	Szpital Uniwersytecki nr 2 im. Dr Jana Biziela w Bydgoszczy Klinika Reumatologii i Układowych Chorób Tkanki Łącznej ul. Ujejskiego 75, 85-168 Bydgoszcz, Poland
408	Joanna Hilt	Centrum Terapii Współczesnej Kopcińskiego 21, 90-242 Łódź, Poland
409	Ewa Kaliszuk-Kamińska	RCMed Długa 2, 09-505 Nowy Duninów, Poland
410	Nonna Nowak	ClinicMed Badurski i wspólnicy Spółka Jawna, Stołeczna 7/200, 15-879 Białystok, Poland
411	Krystyna Kuć	KLIMED Marek Klimkiewicz , Konstytucji 3 Maja 24/5, Białystok 15-776, Poland
412	Wojciech Bąkowski	KLIMED Marek Klimkiewicz , Ks. Janusza I 13, 18-404 Łomża, Poland
413	Małgorzata Socik-Pojawa	Medycyna Kliniczna Koszykowa 59/7 Street, 00-0060 Warszawa, Poland
414	Maria Rell-Bakalarska	Rheuma Medicus ZOZ Pruszkowska 6, 02-118 Warszawa, Poland
801	Milen Karagyozov, MD	MHAT Trimontium OOD; Department of Internal Diseases; 126, "Tsar Boris III Obedinitel" Str., 4000 Plovdiv, Bulgaria
802	Krasimira Stanimirova, MD	MHAT Lyulin EAD; Department of Rheumatology; 81, “Petar Dertliev” Blvd., Lyulin 6; 1336 Sofia, Bulgaria
803	Stoyan Todorov, MD	MHAT – Shumen AD; 5th floor, First Internal Department; 63, “Vasil Aprilov” Str.; 9700 Shumen, Bulgaria
804	Tsvetanka Petranova , MD	Medical Center Excelsior OOD; 4, Golo bardo Str; 1000, Sofia, Bulgaria
805	Daniela Bichovska, MD	Medical Center Synexus Sofia EOOD; 20A, “Andrey Saharov” Blvd.; “Mladost 1” District, 1784, Sofia, Bulgaria
806	Margarita Velkova, MD	Medical Center - Teodora EOOD; 101, “Mutkurova” Str.; 7000 Ruse, Bulgaria
807	Dimitar Penev, MD	UMHAT - Kaspela EOOD; Clinic of Rheumatology; 64, “Sofia” Blvd.; 4000 Plovdiv, Bulgaria
808	Ivan Goranov, MD	MHAT - Plovdiv AD; Department of rheumatology; 234, “Bulgaria” Blvd.; 4003 Plovdiv, Bulgaria
809	Rodina Licheva, MD	“DCC XVII–Sofia” EOOD; 108, “Evlogi Georgiev” Blvd.; 1505 Sofia, Bulgaria
810	Boycho Oparanov, MD	Military Medical Academy, MHAT – Sofia; Department of Rheumatology; 3, Sv. Georgi Sofiyski Str.; 1606 Sofia, Bulgaria
811	Prof. Rumen Stoilov, MD	UMHAT “Sv. Ivan Rilski” EAD; Clinic of Rheumatology; 13, “Urvich” Str.; 1612 Sofia, Bulgaria
812	Prof. Rasho Rashkov, MD	UMHAT “Sv. Ivan Rilski” EAD; Clinic of Rheumatology; 13, “Urvich” Str.; 1612 Sofia, Bulgaria
814	Nadezhda Kapandjieva, MD	UMHAT – Ruse AD; First Department of Internal Diseases; 2, “Nezavisimost” Str.; 7002 Ruse, Bulgaria

Online Resource 2 Full exclusion criteria

Subjects were not eligible for this study if they fulfilled any of the following exclusion criteria:

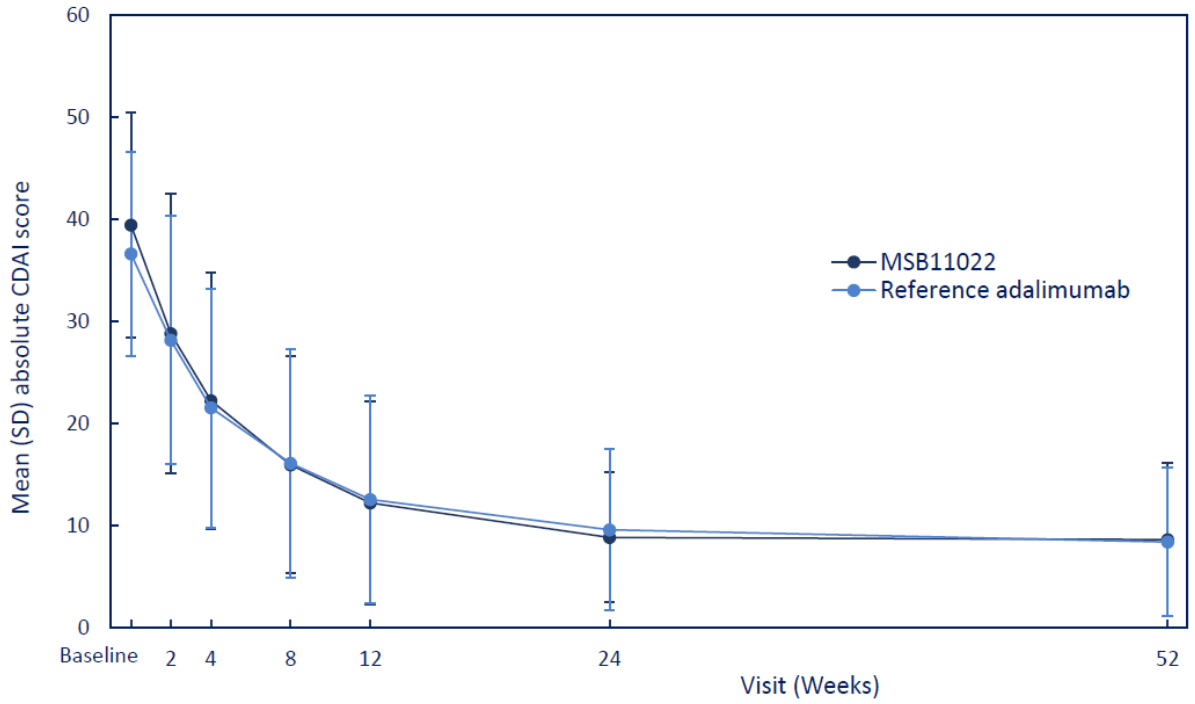
1. American College of Rheumatology (ACR) functional class IV as defined by the ACR classification of functional status or wheelchair/bedbound.
2. A diagnosis of Felty's syndrome.
3. A diagnosis of any other inflammatory arthritides/systemic autoimmune disease other than secondary Sjögren's syndrome.
4. Received therapy with leflunomide within 12 weeks prior to baseline unless subject had undergone a drug elimination procedure with cholestyramine or activated charcoal powder, in which case the wash-out period was a minimum of 4 weeks.
5. Received disease-modifying antirheumatic drugs (DMARDs) other than methotrexate (MTX) including but not limited to oral or injectable gold, sulfasalazine, azathioprine, penicillamine, cyclosporine, or tacrolimus within 4 weeks prior to baseline. Subjects could have been taking oral hydroxychloroquine provided that the dose was not greater than 400 mg/day, or chloroquine provided that the dose was not greater than 250 mg/day and that doses had been stable for a minimum of 12 weeks prior to baseline. The hydroxychloroquine or chloroquine treatment needed to be continued at a stable dose for the duration of the study.
6. Received increasing doses of nonsteroidal anti-inflammatory drugs (NSAIDs) (including low-dose aspirin and Cyclooxygenase-2 [COX-2] inhibitors) in the 2 weeks prior to baseline.
7. Prior exposure to alkylating agents, such as chlorambucil or cyclophosphamide.
8. Used oral glucocorticoids >10 mg/day prednisone or equivalent. Doses up to 10 mg/day were allowed if had been kept stable for the 4 weeks prior to baseline.
9. Any intra-articular, intravenous, or intramuscular use of corticosteroids in the 6 weeks prior to baseline.
10. High-potency opioid analgesics (e.g., methadone, hydromorphone, oxycodone, fentanyl, or morphine) were prohibited during the study; other analgesics were allowed (e.g., propoxyphene, tramadol, codeine, or aspirin), although not within 12 hours of study visits.
11. History of tuberculosis (TB), presence of active TB, or latent TB as detected by imaging (e.g., chest X-ray, chest computed tomography [CT] scan, magnetic resonance imaging [MRI]) and/or positive QuantiFERON-TB Gold test (QFT) and/or clinical examination or had had latent TB disease at any time in the past. Subjects were evaluated for latent TB infection (LTBI) by the QFT enzyme-linked immunosorbent assay and by chest X-ray. If a subject tested positive for LTBI at screening, the subject was screen-failed and was not randomized. Subjects with indeterminate QFT test result could have been retested once within the screening period:
    a. If the retest was negative, the subject was eligible to take part in the study.
    b. If the retest was positive, the subject was not eligible to participate in the study.
    c. If the retest was again indeterminate, the subject was considered as having LTBI and was not eligible to participate in the study. No further QFT was to be performed.
12. Received a live vaccine within 3 months prior to investigational medicinal product (IMP) administration or intended to receive a live vaccination during the study or within 3 months after the last dose of IMP.

13. History of hypersensitivity to any component of the IMP formulation, comparable drugs, or latex.
14. Any infection as follows:
    a. Required treatment with oral antibiotics within 14 days prior to IMP administration.
    b. A serious infection defined as requiring hospitalization or treatment with intravenous antibiotics within 8 weeks prior to IMP administration.
    c. Had herpes zoster or any opportunistic infection (e.g., histoplasmosis, coccidioidomycosis, blastomycosis, pneumocystis, listeriosis, legionellosis, or parasitic infections) within 6 months prior to administration of IMP.
    d. A history of persistent chronic infection or recurrent infections (3 or more of the same type of infection in any rolling 12-month period, e.g., urinary tract or upper respiratory tract infections).
    e. Had documentation of seropositivity for human immunodeficiency virus (HIV), or positive hepatitis C antibody test or hepatitis B surface antigen test and/or core antibody test for immunoglobulin (Ig) G and/or IgM or total Ig at screening.
15. History of lymphoproliferative disease or previous malignancy. Curatively treated basal or squamous cell carcinomas of the skin were not excluded, unless they occurred within 12 months of randomization. Curatively treated localized in situ carcinoma of the cervix was also not excluded, if there was no evidence of recurrence within the last 5 years prior to randomization.
16. Had a poorly controlled medical condition, such as but not limited to, poorly controlled diabetes, unstable ischemic heart disease, uncontrolled hypertension (systolic ≥160 mmHg and/or diastolic ≥95 mmHg), or other relevant medical disease, such as a neurological, pulmonary, gastrointestinal, or endocrine disease or a history of clinically significant hematological, renal, or liver disease or any other condition that, in the opinion of the Investigator, would have put the subject at risk by participation in the study.
17. Any major surgery (including arthroplasty) performed within the 6 weeks prior to the first dose of IMP.
18. Had presence of a solid organ or bone marrow transplant (with the exception of a successful corneal transplant >3 months prior to screening).
19. Had a concomitant diagnosis or history of congestive heart failure (New York Heart Association [NYHA] class III or IV).
20. Had a known history, family history of, or symptoms consistent with a demyelinating disease, such as multiple sclerosis or optic neuritis, or symptoms suggestive of such a disorder.
21. Laboratory abnormalities deemed clinically significant by the Investigator or any of the following at screening:
    a. Hemoglobin <8 g/dl for women or 8.5 g/dl for men.
    b. White blood cells (WBCs) $<3.5 \times 10^9$/l
    c. Absolute neutrophil count (ANC) $<1.5 \times 10^9$/l.
    d. Platelet count $<100 \times 10^9$/l.
    e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN).
    f. Creatinine >1.5 mg/dl if <65 years old, or >ULN if ≥65 or with proteinuria 4+ or greater by dipstick.

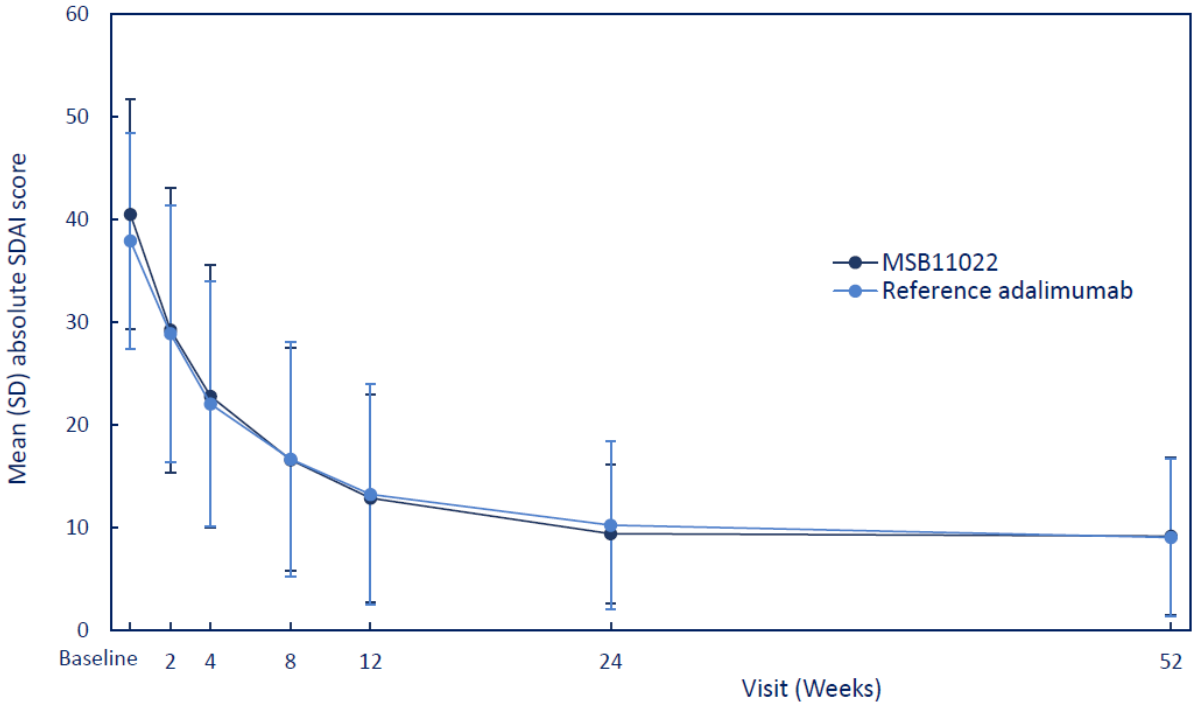
22. Women who were pregnant, lactating, or planning pregnancy within 6 months after the last dose of IMP.
23. Legal incapacity or limited legal capacity.
24. Subject was considered by the Investigator, for any reason, to be an unsuitable candidate for the study.
25. Subject had participated in any non-biological investigational clinical study within 12 weeks or 5 drug half-lives (whichever was longer) before first administration of IMP in this study or planned intake of an investigational drug during the course of this study.
26. History of clinically significant drug or alcohol abuse within the last 2 years.

Online Resource 3 Mean (SD) CDAI (a) and SDAI (b) scores (ITT analysis set)

(a)



(b)



CDAI Clinical Disease Activity Index, *SD* standard deviation, *SDAI* Simple Disease Activity Index

Online Resource 4 Improvements in QoL scores from baseline (ITT analysis set)

Assessment	Visit	MSB11022 (*N* = 143)		Reference adalimumab (*N* = 145)	
		Absolute, mean (SD)	Absolute change from baseline, mean (SD)	Absolute, mean (SD)	Absolute change from baseline, mean (SD)
EQ-5D-5L index value	Week 12	0.77 (0.14)	0.17 (0.18)	0.77 (0.14)	0.15 (0.17)
	Week 24	0.79 (0.15)	0.19 (0.21)	0.79 (0.15)	0.18 (0.18)
	Week 52	0.80 (0.16)	0.21 (0.20)	0.81 (0.14)	0.20 (0.18)
EQ-5D-5L VAS	Week 12	64.6 (19.64)	22.0 (25.91)	63.2 (20.96)	18.0 (23.89)
	Week 24	66.2 (22.19)	24.1 (26.99)	65.6 (24.25)	18.6 (26.58)
	Week 52	68.8 (21.66)	26.8 (26.15)	69.0 (22.65)	22.6 (24.93)
HAQ-DI score	Week 12	1.10 (0.59)	−0.53 (0.54)	1.13 (0.61)	−0.51 (0.47)
	Week 24	1.03 (0.64)	−0.61 (0.60)	1.01 (0.64)	−0.62 (0.58)
	Week 52	0.95 (0.69)	−0.68 (0.68)	0.98 (0.65)	−0.65 (0.65)
SF-36 score (Physical component Score)	Week 12	39.04 (7.90)	8.76 (7.99)	38.65 (8.58)	8.02 (6.51)
	Week 24	40.51 (8.82)	10.23 (9.03)	40.79 (9.15)	9.99 (8.29)
	Week 52	41.75 (9.51)	11.56 (9.33)	41.59 (9.33)	11.15 (8.66)

EQ-5D-5L EuroQOL 5D-5L, *HAQ-DI* Health Assessment Questionnaire Disability Index, *QoL* quality of life, *SD* standard deviation, *SF-36* Short Form (36) Health Survey

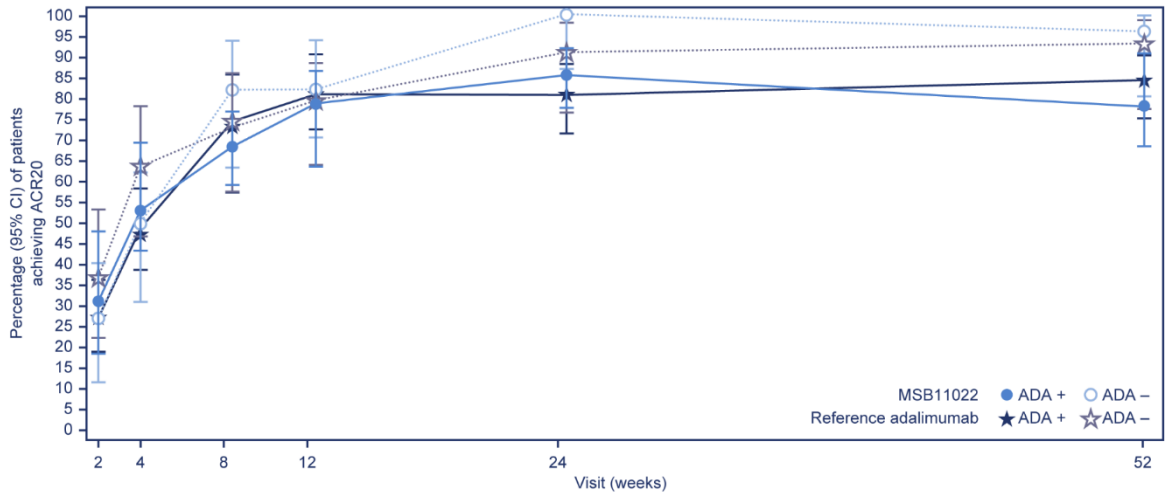
Online Resource 5 Injection site pain VAS Scores at weeks 4, 6, and 8 (safety analysis set)

Assessment	Visit	MSB11022 (*N* = 143)		Reference adalimumab (*N* = 145)	
		Absolute, mean (SD)	Absolute change from week 4, mean (SD)	Absolute, mean (SD)	Absolute change from week 4, mean (SD)
Immediately post-injection	Week 4	3.0 (8.4)	–	6.4 (14.3)	–
	Week 6	1.6 (5.5)	−1.4 (5.1)	5.3 (14.3)	−1.3 (10.2)
	Week 8	1.3 (3.9)	−1.7 (6.5)	4.6 (12.6)	−2.3 (10.4)
15 minutes post-injection	Week 4	0.6 (2.5)	–	1.7 (7.6)	–
	Week 6	0.3 (1.1)	−0.2 (2.7)	2.1 (8.8)	0.4 (3.3)
	Week 8	0.3 (1.0)	−0.3 (2.3)	1.1 (4.9)	−0.7 (4.1)
1 hour post-injection	Week 4	0.1 (0.6)	–	0.8 (5.6)	–
	Week 6	0.1 (0.3)	0.0 (0.7)	0.8 (5.7)	0.0 (2.7)
	Week 8	0.0 (0.3)	−0.1 (0.6)	0.1 (0.8)	−0.7 (5.4)

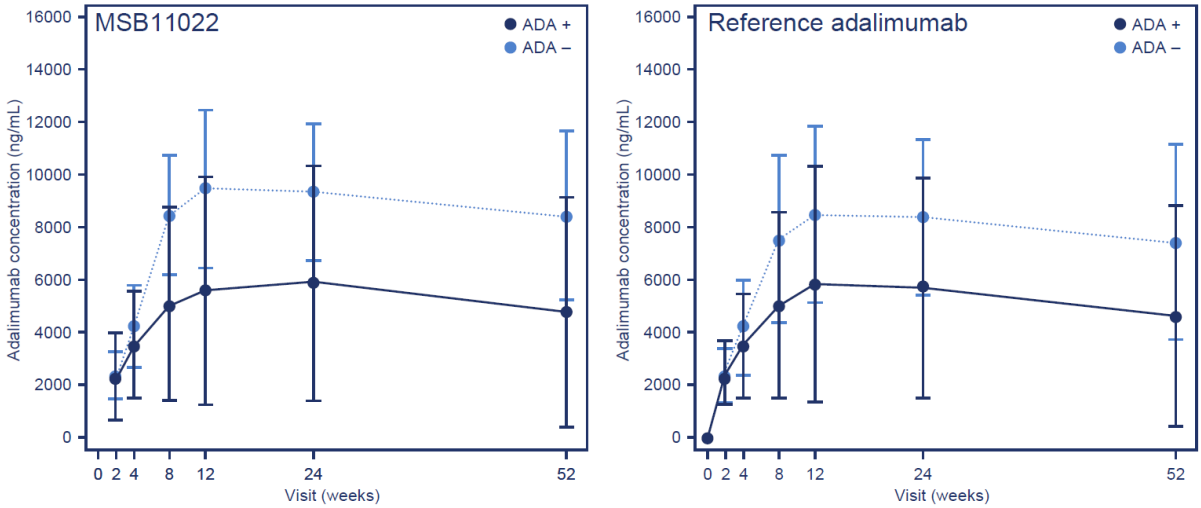
VAS visual analogue scale

Online Resource 6 Percentage (95% CI) of patients achieving ACR20 response (a) and mean (SD) trough adalimumab concentrations (b) by ADA status (safety analysis set)

(a)



(b)



ACR20 ≥20% improvement in American College of Rheumatology response, *ADA* antidrug antibody, *SD* standard deviation