Εμφάνιση ΙΦΝΕ ή ΣπΑ σε ασθενείς που λαμβάνουν βιολογική θεραπεία για τη μία από τις δύο νόσους

Διαφορές σε σχέση με την προ βιολογικών παραγόντων εποχή

Το παράδειγμα του Adalimumab και του βιοομοειδούς MSB 11022

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Disclosure statement

My Travel and Accommodation expenses are covered by
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Spondyloarthritis (SpA) and IBD

- Spondyloarthritis (SpA)- a family of chronic immune-mediated inflammatory joint diseases.
- One of their distinguishing characteristics are frequent extra-articular manifestations (EAMs).
- SpAs have been historically subcategorized into discrete disease entities, including ankylosing spondylitis (AS), psoriatic arthritis (PsA), and enteropathic arthritis.
- However, there is increasing recognition of these as overlapping diseases on a continuum.
- ASAS (Assessment of SpondyloArthritis Society) criteria now classifies SpAs based on clinical features, either as axial SpA (axSpA) or peripheral SpA (pSpA).
- ASAS also recognises the prevalence and significance of inflammatory bowel disease (IBD) in SpA and have incorporated coexisting IBD as a classification criterion

Proft F and Poddubnyy D. *Ther Adv Musculoskelet Dis* 2018; 10: 129–139.

National Institute for Health and Care Excellence (UK). https://www.nice.org.uk/ guidance/ng65 (2017; 22 April 2020).

Fragoulis GE, Liava C, Daoussis D, *World J Gastroenterol* 2019; 25: 2162–2176.

Spondyloarthritis (SpA) and IBD

- Η αλληλεπικάλυψη μεταξύ SpA και IBD είναι τεκμηριωμένη και οι επιδημιολογικές μελέτες έχουν δείξει σταθερά μια συσχέτιση μεταξύ αυτών των ασθενειών

- Βιβλιογραφία ΙΦΝΕ

Ακτινολογική ιερολαγονίτιδα τεκμηριώνεται στο **20–50% των ΙΦΝΕ ασθενών και επιδεινούμενη AS στο 1–10%**

Harbord M ετ αλ European Crohn's and Colitis Organisation *J Crohns Colitis* 2016; 10: 239–254.

5. Kopylov *et al*. *J Rheumatol* 2018; 45: 498–505.

Spondyloarthritis (SpA) and IBD

- Higher joint activity scores [both the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Metrology Index (BASMI)] are independently predictive of microscopic GI inflammation in SpA patients Van Praet et al. Ann Rheum Dis 2013; 72: 414–417

- There is a mismatch between patients' clinical symptoms and their GI inflammatory activity, and even macroscopic lesions are frequently asymptomatic Kopylov et al. J Rheumatol 2018; 45: 498–505

- Some studies have labelled this phenomenon as 'silent IBD', although this terminology is misleading, as there is insufficient evidence to suggest these asymptomatic lesions are definite precursors to overt IBD

Leirisalo-Repo M Stenman *Arthritis Rheum* 1994; 37: 23–31

Lifetime IBD risk in patients with SpA

Cohort studies and meta-analyses quote a lifetime IBD risk of between 4% and 14% in patients with SpA

Stolwijk, C et al Ann Rheum Dis 2015; 74: 65–73.

De Winter, JJ et al Arthritis Res Ther 2016; 18: 196.

A prospective Belgian study of 123 patients with SpA followed over a mean period of 62 months found 7% of patients developed *de novo* IBD

De Vos et al. Gastroenterology 1996; 110: 1696–1703

Spondyloarthritis (SpA) and IBD

- A large population-based matched cohort study of 4101 AS patients matched with 28,591 controls found 4% of patients had a pre-existing diagnosis of IBD, increasing to 7.5% at the end of 20-year follow up

Stolwijk S et al Ann Rheum Dis 2015; 74: 1373–1378

Infliximab in IBD

- **Infliximab** is **effective** in inducing and maintaining remission in UC evidenced in the **ACT 1** and **ACT 2** trials, as well as in CD evidenced in the **ACCENT 1** trial.
- The **SONIC** trial demonstrated ***infliximab in combination with 2.5 mg/kg azathioprine*** was more successful in achieving clinical and endoscopic remission compared with infliximab monotherapy at week 26.
- Subsequently, studies have shown ***immunomodulators (such as thiopurines and methotrexate) improve the pharmacokinetics of infliximab*** and are associated with reduced infliximab clearance.
- The PANTS study found low anti-TNF drug levels at week 14 predicted non-remission at week 54, ***commonly due to the development of immunogenicity and presence of anti-TNF antibodies*.**
- The ***addition of an immunomodulator mitigates the risk of immunogenicity*** hence risk of treatment failure

Infliximab versus adalimumab

A **systematic review** in 2018 found infliximab had considerably greater immunogenicity compared with adalimumab, highlighting the role of co-prescription of infliximab with an immunomodulator.

Vermeire, et al. Immunogenicity of biologics in inflammatory bowel disease. Therap Adv Gastroenterol 2018

Adalimumab in IBD

- Adalimumab is effective in inducing and maintaining long-term remission in UC, evidenced in the ULTRA1, ULTRA2 and ULTRA3 trials, as well as in CD, evidenced in the CLASSIC 1, CHARM and EXTEND trials.
- The typical induction regime used in IBD is 160 mg at week 0 followed by 80 mg at week 2. Escalation of maintenance treatment from 40 mg fortnightly dosing to weekly dosing can be helpful in recapturing response.

Adalimumab in IBD

- Unlike **infliximab**, meta-analyses have shown no benefit in adding an immunomodulator to **adalimumab** in inducing or maintaining remission.

Chalhoub, JM, et al. Inflamm Bowel Dis 2017; 23: 1316–1327

- The **exception** to this, however, is **when a patient is switched to adalimumab after developing infliximab antibodies**, given the **higher risk of *de novo* adalimumab antibodies** in this group

Frederiksen, MT, et al. Inflamm Bowel Dis 2014; 20: 1714–1721

- IBD patients with immune-mediated loss of response to anti-TNF have improved clinical outcomes when azathioprine is added to their second anti-TNF. The majority of patients in this study were switched from infliximab to adalimumab

Roblin, X Gut 2020

Infliximab in IBD

- There is increasing evidence in the IBD literature on the use of therapeutic drug monitoring (TDM) through infliximab trough measurements, and dose optimization to reach a target trough range.
- This can be achieved by increasing infliximab dose to 10 mg/kg and/or shortening infusion intervals to a minimum of 4 weeks.
- The TAXIT and TAILORIX trials compared dose optimization based on TDM with clinical features alone and found no difference in rates of clinical remission at 1 year. However, the TAXIT trial demonstrated fewer IBD flares in the TDM group. There is also increasing evidence that TDM leads to most cost-effective use of infliximab.
- Subcutaneous infliximab has recently been approved for use in rheumatoid arthritis and is the subject of an encouraging switch study in IBD. Results from 1 year suggest similar efficacy and safety compared with intravenous infliximab, with potentially favourable pharmacokinetics.
- Phase III trials are ongoing, and subcutaneous infliximab may prove to be an attractive future treatment option for IBD.

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The IL17-axis inhibition

Gut Online First, published on May 17, 2012 as 10.1136/gutjnl-2011-301668

ORIGINAL ARTICLE

Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial

Wolfgang Hueber,[1] Bruce E Sands,[2] Steve Lewitzky,[3] Marc Vandemeulebroecke,[4] Walter Reinisch,[5] Peter D R Higgins,[6] Jan Wehkamp,[7] Brian G Feagan,[8] Michael D Yao,[9] Marek Karczewski,[10] Jacek Karczewski,[10] Nicole Pezous,[4] Stephan Bek,[1] Gerard Bruin,[1] Bjoern Mellgard,[1] Claudia Berger,[1] Marco Londei,[11] Arthur P Bertolino,[1] Gervais Tougas,[4] Simon P L Travis,[12] for the Secukinumab in Crohn's Disease Study Group

Contrary to the initial hypothesis that IL-17 blockade would also improve IBD activity, a CD trial unexpectedly showed that secukinumab paradoxically worsened CD activity, and the trial was terminated prematurely.

Of the seven SAEs suspected to be drug related, five were cases of worsening of Crohn's disease, four on secukinumab (4/39 CD patients) and one on placebo.

Exacerbation of IBD in anti-IL17A treated patients with psoriasis

In a pooled analysis of phase II and III clinical trials of secukinumab for plaque psoriasis, there were 9 new-onset cases or exacerbations of IBD (incidence rate of 0.33 per 100 patients per year), compared with 1 in etanercept control groups (incidence rate of 0.34 per 100 patients per year).

The authors' analysis concluded that there is no meaningful clinical relationship between secukinumab and IBD

van de Kerkhoff P et al J Am Acad Dermatol. 2015;373(26):2534-2548

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis

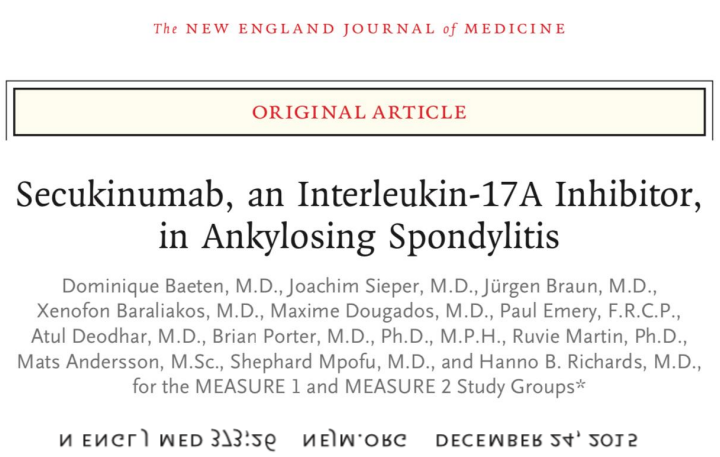
Dominique Baeten, M.D., Joachim Sieper, M.D., Jürgen Braun, M.D., Xenofon Baraliakos, M.D., Maxime Dougados, M.D., Paul Emery, F.R.C.P., Atul Deodhar, M.D., Brian Porter, M.D., Ph.D., M.P.H., Ruvie Martin, Ph.D., Mats Andersson, M.Sc., Shephard Mpofu, M.D., and Hanno B. Richards, M.D., for the MEASURE 1 and MEASURE 2 Study Groups*

N ENGL J MED 373;26 NEJM.ORG DECEMBER 24, 2015

New-onset IBD and/or exacerbations occurred in 5 patients receiving secukinumab (incidence rate of 0.7 per 100 patients per year) compared with 0 in placebo groups

- Crohn’s disease was an adverse event in three patients in the group receiving subcutaneous secukinumab at a dose of 75 mg in MEASURE 1. Two cases were in patients with a history of Crohn’s disease, and one was in a patient with a history of a polyp and an adenoma in the colon;
- All three cases were nonserious.
- Crohn’s disease was a serious adverse event in two patients receiving subcutaneous secukinumab in MEASURE 2 (one each in the 75-mg and 150-mg groups); the patient receiving the lower dose of secukinumab was considered to have an exacerbation of preexisting Crohn’s disease related to the study treatment, and this resulted in discontinuation.

- The pooled exposure-adjusted incidence rate of Crohn’s disease across both studies was 0.7 events per 100 patient-years of exposure to secukinumab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Exacerbation of IBD after biologic treatment given for another indication

REVIEWS

Management of psoriasis in patients with inflammatory bowel disease: From the Medical Board of the National Psoriasis Foundation

Scott M. Whitlock, MD,[a] Clinton W. Enos, MD,[a] April W. Armstrong, MD, MPH,[b] Alice Gottlieb, MD,[c] Richard G. Langley, MD,[d] Mark Lebwohl, MD,[e] Joseph F. Merola, MD, MMSc,[f] Caitriona Ryan, MD,[g] Michael P. Siegel, PhD,[h] Jeffrey M. Weinberg, MD,[e] Jashin J. Wu, MD,[i] and Abby S. Van Voorhees, MD[a]
Norfolk, Virginia; Los Angeles, California; Valhalla and New York, New York; Halifax, Nova Scotia, Canada; Boston, Massachusetts; Dallas, Texas; and Portland, Oregon

CAPSULE SUMMARY

- There is a significant association between psoriasis and inflammatory bowel disease.
- Infliximab and adalimumab have demonstrated efficacy in psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease.
- Because of the possible association of interleukin 17 inhibitors with inflammatory bowel disease, caution should be exercised in using these agents in this patient population.

Case Reports > J Crohns Colitis. 2018 Aug 29;12(9):1131-1133. doi: 10.1093/ecco-jcc/jjy063.

Emergence of Inflammatory Bowel Disease During Treatment With Secukinumab

María José Fobelo Lozano [1], Reyes Serrano Giménez [1], Manuel Castro Fernández [2]

Affiliations + expand

PMID: 29746636 DOI: 10.1093/ecco-jcc/jjy063

SPC Secukinumab

1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ

Cosentyx 150 mg κόνις για ενέσιμο διάλυμα

4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση

Νόσος του Crohn

Απαιτείται προσοχή όταν το Cosentyx συνταγογραφείται σε ασθενείς με νόσο του Crohn καθώς παρατηρήθηκαν εξάρσεις της νόσου του Crohn, οι οποίες σε ορισμένες περιπτώσεις ήταν σοβαρές, σε κλινικές μελέτες τόσο στην ομάδα του Cosentyx όσο και στην ομάδα του εικονικού φαρμάκου. Οι ασθενείς, οι οποίοι λαμβάνουν θεραπεία με Cosentyx και έχουν νόσο του Crohn θα πρέπει να παρακολουθούνται στενά.

OPEN ACCESS

CLINICAL SCIENCE

Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials

Stefan Schreiber,[1] Jean-Frederic Colombel,[2] Brian G Feagan,[3] Kristian Reich,[4] Atul A Deodhar,[5] Iain B McInnes,[6] Brian Porter,[7] Ayan Das Gupta,[8] Luminita Pricop,[9] Todd Fox[7]

BMJ Schreiber S, *et al*. *Ann Rheum Dis* 2019;**78**:473–479. doi:10.1136/annrheumdis-2018-214273 eular

Author affiliations
[1]University Hospital Schleswig Holstein, Christian-Alrechts-University, Kiel, Germany
[2]Icahn School of Medicine at Mount Sinai, New York City, New York, USA
[3]Robarts Clinical Trials, Western University, London, Ontario, Canada
[4]Dermatologikum Berlin and SCIderm Research Institute, Hamburg, Germany
[5]Oregon Health & Science University, Portland, Oregon, USA
[6]University of Glasgow, Glasgow, UK
[7]Novartis Pharma AG, Basel, Switzerland
[8]Novartis Healthcare Pvt. Ltd, Hyderabad, Telangana, India
[9]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

What does this study add?

- This manuscript includes data from a large safety analysis (n=7355; cumulative exposure=16 2260.9) across 21 clinical trials, spanning up to 5 years of treatment for PsO and PsA and up to 4 years in AS. Additionally, available postmarketing safety surveillance data are also included.
- IBD events were uncommon with secukinumab treatment and the observed exposure adjusted incidence rates of IBD did not increase over time.

How might this impact on clinical practice or future developments?

- This manuscript adds clinically meaningful evidence regarding the observed incidence rates of IBD in patients with PsO, PsA and AS treated with secukinumab.

Συχνές Ερωτήσεις

- **What are biosimilars?**
- **Is it possible to distinguish an originator from a biosimilar prescription?**
- **How are biosimilars approved?**
- **Is there controlled trial evidence for the use of biosimilars in IBD?**
- **What has been the real-world experience with IBD biosimilars from a safety and efficacy standpoint?**
- **Are biosimilars considered interchangeable with the reference product? Who determines what version of the drug my patient will get?**
- **What is the position of gastroenterology societies and patient advocacy societies on switching from the originator to a biosimilar product for IBD?**

Συχνές Ερωτήσεις

- **Τι είναι τα βιομοειδή;**
- **Είναι δυνατόν να γίνει διάκριση του προϊόντος αναφοράς από ένα βιομοειδές;**
- **Πώς εγκρίνονται τα βιομοειδή;**
- **Υπάρχουν ελεγχόμενες clinical trials για τη χρήση των βιομοειδών στις ΙΦΝΕ;**
- **Ποια είναι η real world experience με τα βιομοειδή στις ΙΦΝΕ πραγματική εμπειρία με τα βιομοειδή από άποψη ασφάλειας και αποτελεσματικότητας;**
- **Θεωρούνται ανταλλάξιμα τα βιομοειδή με το προϊόν αναφοράς;**
- **Ποιος καθορίζει ποια έκδοση του φαρμάκου θα πάρει ο ασθενής μου;**
- **Ποια είναι η θέση των γαστρεντερολογικών εταιρειών και των εταιρειών υπεράσπισης ασθενών/συλλόγων ασθενών κατά τη μετάβαση από το προϊόν αναφοράς σε ένα βιομοειδές για τις ΙΦΝΕ;**

Ανταλλαξιμότητα - Αυτόματη αντικατάσταση (interchangeability) βιομοειδών φαρμάκων

- Παρόλο που τα **βιομοειδή** θεωρούνται **πολύ παρόμοια με το προϊόν αναφοράς**, ***<u>ΔΕΝ θεωρούνται ανταλλάξιμα</u>***.
- Η **ανταλλαξιμότητα** όπως ορίζεται από το FDA και τον EMA έχει αυστηρό πρότυπο, υπονοώντας ότι:

1) θα αναμενόταν να παράγει το ίδιο κλινικό αποτέλεσμα **σε κάθε δεδομένο ασθενή** με το αναφερόμενο, &
2) ότι οι κίνδυνοι ασφάλειας ή μειωμένης αποτελεσματικότητας που προκύπτουν από εναλλαγή ή εναλλαγή μεταξύ των προϊόντων δεν είναι μεγαλύτερη από τη χρήση του προϊόντος αναφοράς χωρίς εναλλαγή

ΕΟΦ

- Σύμφωνα με το Κανονιστικό Πλαίσιο που ισχύει σήμερα, δεν συστήνεται η ανταλλαξιμότητα των βιολογικών προϊόντων μεταξύ τους είτε πρόκειται για πρωτότυπα είτε για βιομοειδή

ΕΟΦ

Διότι:

- Ένα φαρμακευτικό βιομοειδες προϊόν είναι «παρόμοιο» με ένα βιολογικό φάρμακο που έχει άδεια κυκλοφορίας. Η δραστική ουσία του βιμοειδούς προϊόντος είναι «παρόμοια» με εκείνη του βιολογικού προϊόντος αναφοράς. Το βιομοειδές και το βιολογικό προϊόν αναφοράς χρησιμοποιούνται κατά κανόνα στην ίδια δόση και για την αντιμετώπιση της ίδιας νόσου.
- Τα βιομοειδή προϊόντα δεν είναι γενόσημα. Το κλασικό παράδειγμα της βιοϊσοδυναμίας δεν μπορεί να εφαρμοστεί σε προϊόντα βιολογικής προέλευσης.

Ποια είναι η θέση των *γαστρεντερολογικών εταιρειών* και των *εταιρειών υπεράσπισης ασθενών* κατά τη μετάβαση από το προϊόν αναφοράς σε ένα παρόμοιο προϊόν (βιομοειδές) για τις ΙΦΝΕ;

European Crohn's and Colitis Organization (ECCO)

Με βάση το Consensus Meeting (2016) «Η μετάβαση από τον προϊόν αναφοράς σε ένα βιομοειδές σε ασθενείς με ΙΦΝΕ είναι αποδεκτή»

Danese S J Crohn's Colitis 2017;11(1):26–34

ECCO

- Τονίζει ότι **λείπουν επιστημονικά και κλινικά στοιχεία** σχετικά με την αντίστροφη εναλλαγή, την πολλαπλή εναλλαγή και τη διασταύρωση μεταξύ των βιομοειδών.
- Υποστηρίζουν ότι οι εναλλαγές πρέπει να εκτελούνται μετά από κατάλληλες συζητήσεις μεταξύ των ασθενών και του γιατρού τους και άλλων ομάδων, μελών.

Ποια είναι η θέση των *γαστρεντερολογικών εταιρειών* και των *εταιρειών υπεράσπισης ασθενών* κατά τη μετάβαση από το προϊόν αναφοράς σε ένα παρόμοιο προϊόν (βιομοειδές) για τις ΙΦΝΕ;

Crohn's and Colitis Foundation

- Δεν αντιτίθεται σε μεμονωμένες μεταβάσεις σταθερών ασθενών **από το προϊόν αναφοράς σε ένα παρόμοιο προϊόν** (ή αντίστροφα), αλλά αντιτίθεται σε πολλαπλές εναλλαγές για φάρμακα που δεν χαρακτηρίζονται ως εναλλάξιμα από το FDA.
- Υποστηρίζει τη διαφάνεια, έτσι ώστε οι ασθενείς και οι πάροχοι να γνωρίζουν ρητά τι προϊόν λαμβάνει ένας ασθενής.

Crohn's and Colitis Foundation. Biosimilars Position Statement

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **82** 983–993

CLINICAL TRIALS

Comparison of the pharmacokinetics, safety, and immunogenicity of MSB11022, a biosimilar of adalimumab, with Humira® in healthy subjects

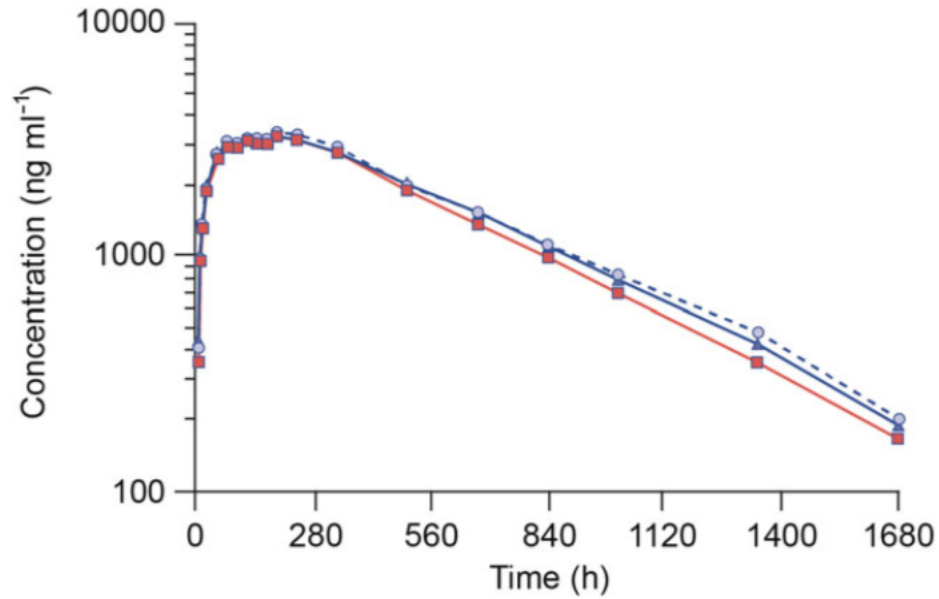

Figure 2

Mean serum concentration–time profiles (on semi-logarithmic scale) by treatment following a single subcutaneous injection of 40 mg MSB11022, US-RP and EU-RMP. Data are presented as means. EU-RMP, EU-reference medicinal product (adalimumab); US-RP, US-reference product (adalimumab).◦ EU-RMP, • MSB11022, • US-RP

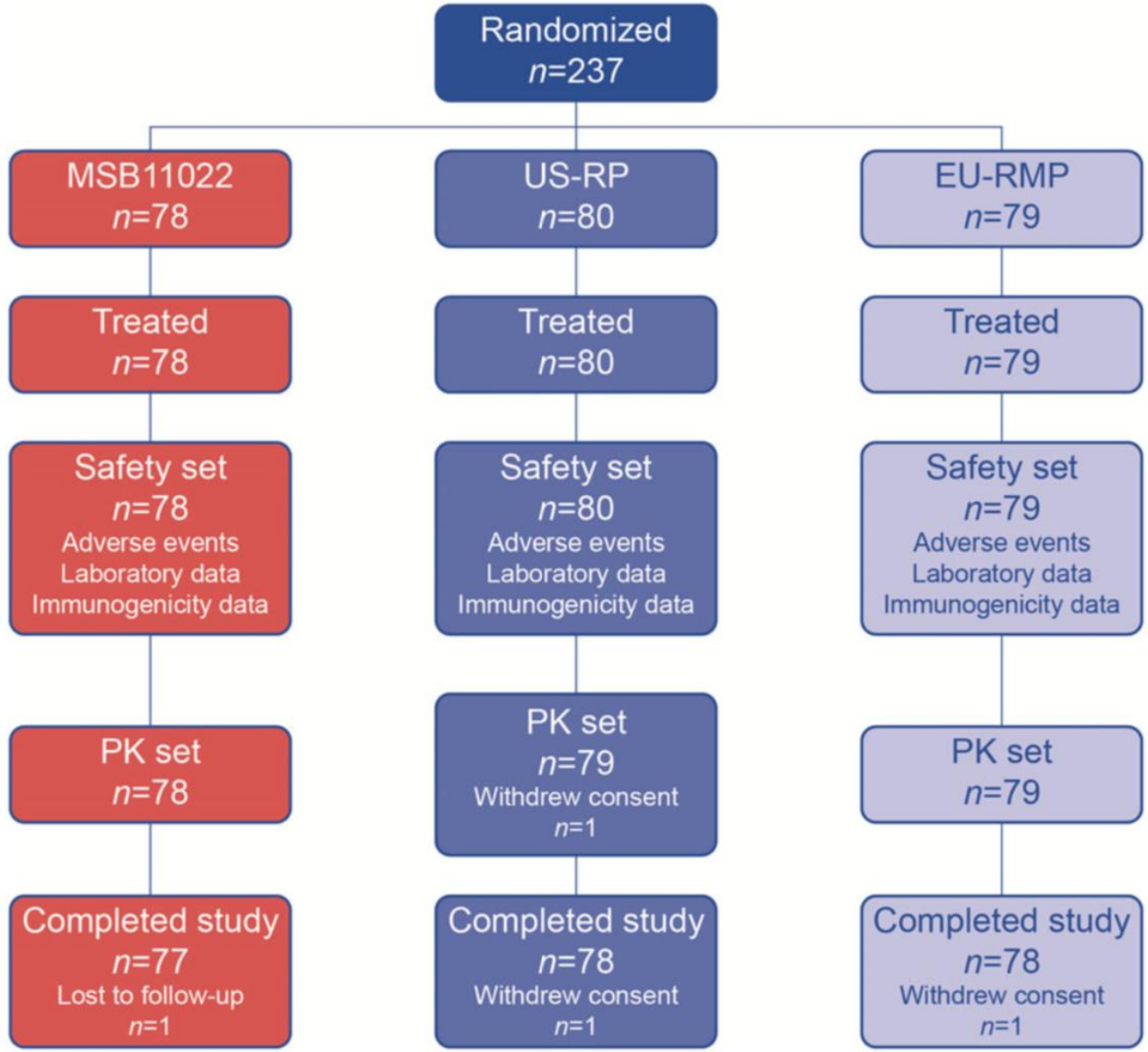

Figure 1

Subject disposition. EU-RMP, EU-reference medicinal product (adalimumab); PK, pharmacokinetic; US-RP, US-reference product (adalimumab)

BJCP British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **82** 983–993 983

CLINICAL TRIALS

Comparison of the pharmacokinetics, safety, and immunogenicity of MSB11022, a biosimilar of adalimumab, with Humira® in healthy subjects

Κύρια Στοιχεία

- Αυτή ήταν η πρώτη κλινική αναφορά ενός νέου προτεινόμενου adalimumab biosimilar, MSB11022 (IDACIO).
- Αυτή η τυχαιοποιημένη, ελεγχόμενη μελέτη φάσης 1 συνέκρινε το PK και την ασφάλεια του MSB11022 έναντι των εγκεκριμένων από τις ΗΠΑ & της Ευρώπης προϊόντος αναφοράς adalimumab.
- Τα αποτελέσματα καταδεικνύουν **βιοϊσοδυναμία** μεταξύ του MSB11022 και των προϊόντων αναφοράς ΗΠΑ / Ευρώπης, καθώς και **αξιόπιστα προφίλ ασφάλειας και ανεκτικότητας**.

Table 4

Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

	MSB11022 *n* = 78			US-RP *n* = 80			EU-RMP *n* = 79		
System organ class preferred term	***n***	**(%)**	**Events**	***n***	**(%)**	**Events**	***n***	**(%)**	**Events**
Subjects with at least one TEAE	49	(62.8)	95	45	(56.3)	82	49	(62.0)	86
Nervous system disorders	15	(19.2)	18	18	(22.5)	24	9	(11.4)	12
Headache	13	(16.7)	16	15	(18.8)	18	7	(8.9)	10
Infections and infestations	18	(23.1)	22	15	(18.8)	15	15	(19.0)	17
Rhinitis	6	(7.7)	6	8	(10.0)	8	3	(3.8)	4
Nasopharyngitis	3	(3.8)	4	4	(5.0)	4	4	(5.1)	5
Upper respiratory tract infection	2	(2.6)	2	2	(2.5)	2	3	(3.8)	3
General disorders and administration site conditions	12	(15.4)	14	8	(10.0)	9	10	(12.7)	12
Injection site pain	3	(3.8)	4	2	(2.5)	2	2	(2.5)	2
Injection site erythema	3	(3.8)	3	1	(1.3)	1	2	(2.5)	2
Injection site pruritus	1	(1.3)	1	1	(1.3)	1	1	(1.3)	1
Injection site bruising	1	(1.3)	1	1	(1.3)	1	0	(0.0)	0
Injection site rash	2	(2.6)	2	0	(0.0)	0	0	(0.0)	0
Fatigue	1	(1.3)	1	0	(0.0)	0	4	(5.1)	4
Gastrointestinal disorders	12	(15.4)	13	9	(11.3)	9	5	(6.3)	6
Toothache	1	(1.3)	1	1	(1.3)	1	2	(2.5)	2
Abdominal discomfort	3	(3.8)	3	1	(1.3)	1	0	(0.0)	0
Musculoskeletal and connective tissue disorders	7	(9.0)	9	5	(6.3)	6	9	(11.4)	10
Arthralgia	0	(0.0)	0	3	(3.8)	3	2	(2.5)	2
Musculoskeletal pain	0	(0.0)	0	1	(1.3)	1	3	(3.8)	3
Respiratory, thoracic and mediastinal disorders	9	(11.5)	9	7	(8.8)	8	7	(8.9)	8
Oropharyngeal pain	7	(9.0)	7	4	(5.0)	4	3	(3.8)	3
Skin and subcutaneous tissue disorders	3	(3.8)	3	7	(8.8)	7	8	(10.1)	10
Injury, poisoning and procedural complications	2	(2.6)	2	2	(2.5)	2	4	(5.1)	4
Eye disorders	0	(0.0)	0	1	(1.3)	1	3	(3.8)	3

EU-RMP, Europe-approved reference medicinal product; TEAE, treatment-emergent adverse event; US-RP, US-licensed reference product.

CLINICAL TRIAL

BJD
British Journal of Dermatology

AURIEL-PsO: a randomized, double-blind phase III equivalence trial to demonstrate the clinical similarity of the proposed biosimilar MSB11022 to reference adalimumab in patients with moderate-to-severe chronic plaque-type psoriasis

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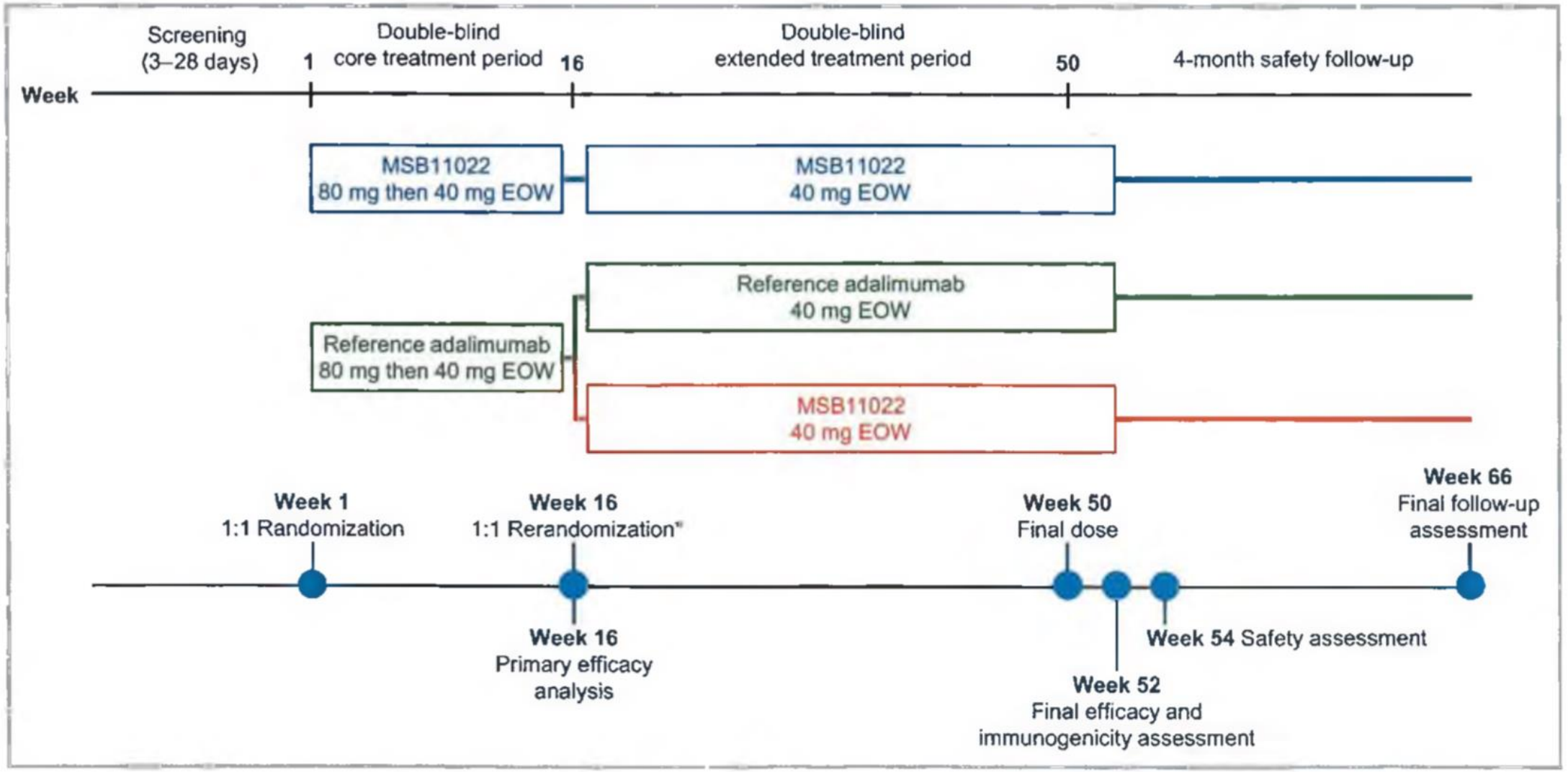
Table 1 Baseline demographic and clinical characteristics (per protocol set)

	MSB11022 (n = 203)	Reference adalimumab (n = 191)
Male, n (%)	136 (67·0)	130 (68·1)
Age (years), mean ± SD	44·8 ± 12·7	42·4 ± 11·8
Race, n (%)		
White	192 (94·6)	179 (93·7)
Black	1 (0·5)	0
Asian	3 (1·5)	8 (4·2)
American Indian or Alaska native	7 (3·4)	4 (2·1)
Region, n	Both arms	
Europe	326	
Americas	68	
Weight (kg), mean ± SD	81·4 ± 13·5	80·0 ± 13·1
Body mass index (kg m^{-2})		
Mean ± SD	26·6 ± 3·1	26·3 ± 3·0
Median (interquartile range)	27·6 (24·2–29·1)	26·8 (24·2–29·1)
PASI		
Mean ± SD	20·6 ± 8·8	21·2 ± 8·1
Median (range)	17·4 (12·0–61·8)	18·4 (12·1–48·2)
BSA affected (%)		
Mean ± SD	28·6 ± 14·3	29·9 ± 13·6
Median (range)	25·9 (11·0–86·0)	27·1 (10·0–72·0)
PGA, n (%)		
Moderate	146 (71·9)	128 (67·0)
Severe	57 (28·1)	63 (33·0)
Previous biologic or other therapy for psoriasis, n (%)	177 (87·2)	168 (88·0)
Previous biologic or other therapy, n (%)		
Etanercept	22 (10·8)	24 (12·6)
Infliximab	2 (1·0)	1 (0·5)
Other	175 (86·2)	166 (86·9)

PASI, Psoriasis Area and Severity Index; BSA, body surface area; PGA, Physician's Global Assessment.


Screening
(3–28 days)
1
Double-blind
core treatment period
16
Double-blind
extended treatment period
50
4-month safety follow-up
Week
MSB11022
80 mg then 40 mg EOW
MSB11022
40 mg EOW
Reference adalimumab
40 mg EOW
Reference adalimumab
80 mg then 40 mg EOW
MSB11022
40 mg EOW
Week 1
1:1 Randomization
Week 16
1:1 Rerandomization*
Week 50
Final dose
Week 66
Final follow-up
assessment
Week 16
Primary efficacy
analysis
Week 54 Safety assessment
Week 52
Final efficacy and
immunogenicity assessment

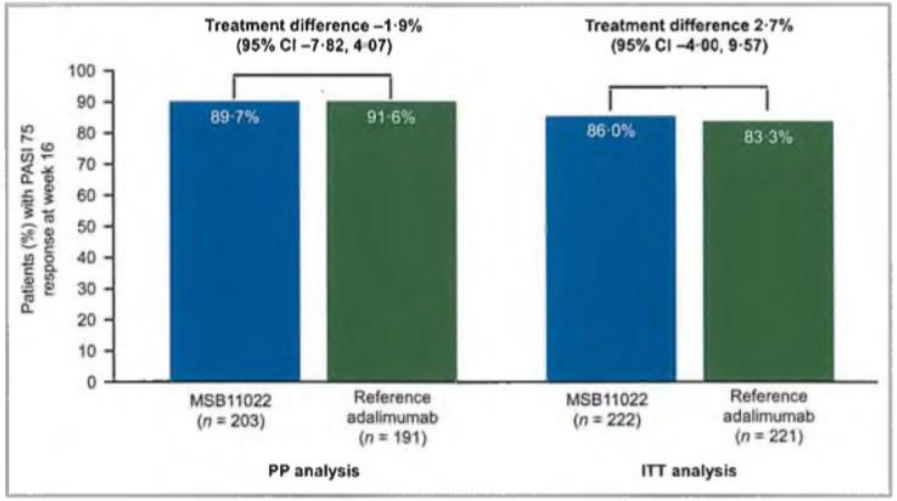


Fig 3. Response rate of ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) at week 16 in the per protocol (PP) and intention-to-treat (ITT) analysis sets. CI, confidence interval.

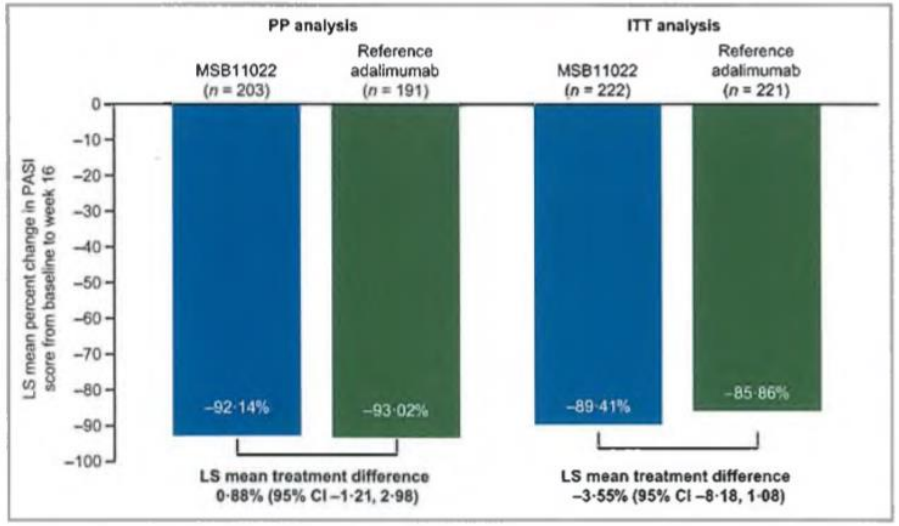
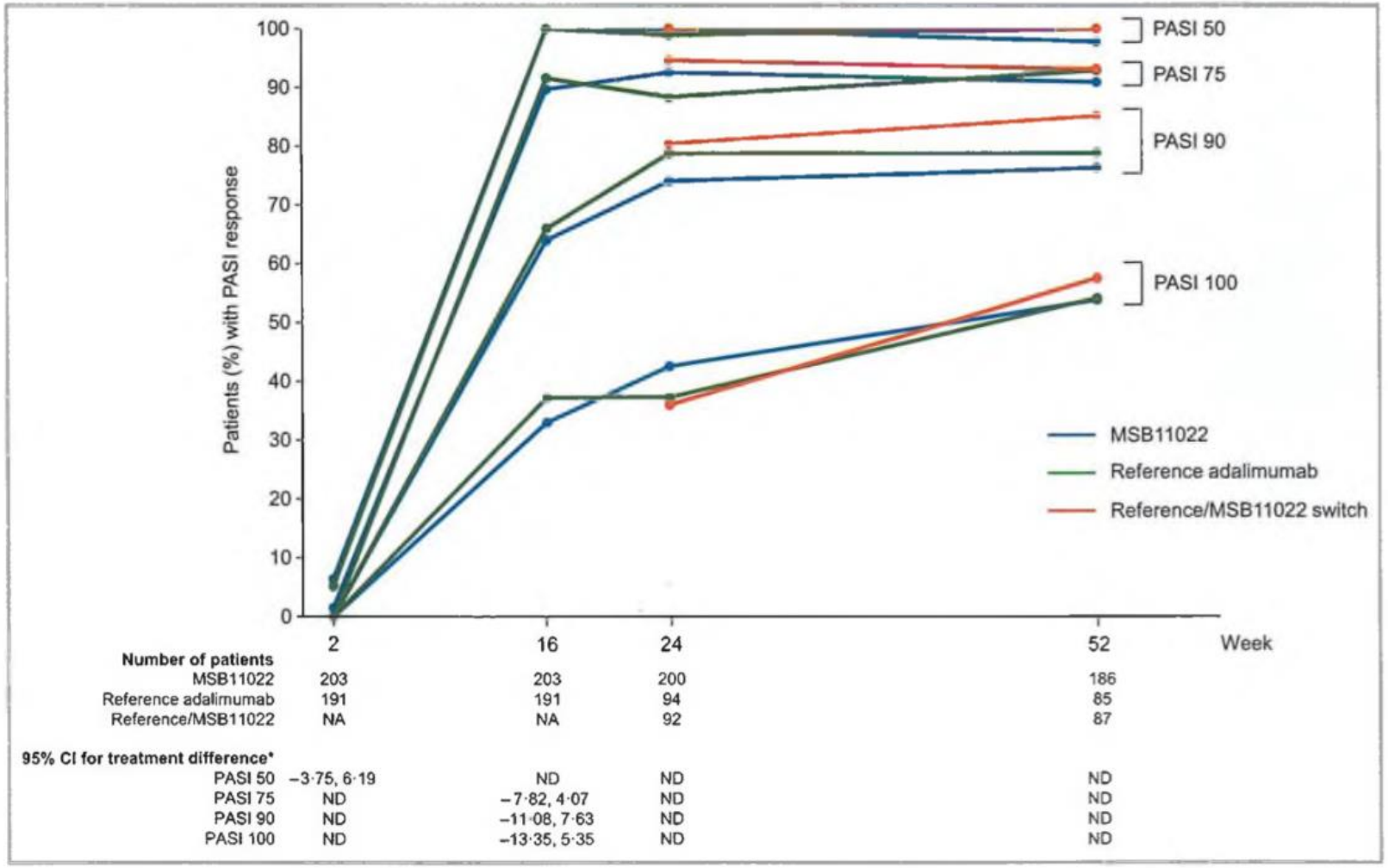


Fig 4. Percentage change in Psoriasis Area and Severity Index (PASI) from baseline to week 16 in the per protocol (PP) and intention-to-treat (ITT) analysis sets. LS, least squares; CI, confidence interval.



Number of patients				
MSB11022	203	203	200	186
Reference adalimumab	191	191	94	85
Reference/MSB11022	NA	NA	92	87
95% CI for treatment difference*				
PASI 50	−3·75, 6·19	ND	ND	ND
PASI 75	ND	−7·82, 4·07	ND	ND
PASI 90	ND	−11·08, 7·63	ND	ND
PASI 100	ND	−13·35, 5·35	ND	ND

Fig 5. Response rates of ≥ 50%, ≥ 75%, ≥ 90% and 100% in Psoriasis Area and Severity Index (PASI 50, 75, 90 and 100) in the per protocol set. *95% confidence interval (CI) for the treatment difference between MSB11022 and reference adalimumab. NA, not applicable; ND, not determined.

Table 3 Treatment-emergent adverse events up to week 66

	MSB11022 (n = 221)	Continued reference adalimumab (n = 119)	Reference/MSB11022 switch (n = 101)
TEAE	173 (78·3)	92 (77·3)	76 (75·2)
Serious TEAE	20 (9·0)	8 (6·7)	5 (5·0)
Treatment-related TEAE	69 (31·2)	41 (34·5)	33 (32·7)
Serious treatment-related TEAE	3 (1·4)	5 (4·2)	0
TEAE of special interest[a]	12 (5·4)	4 (3·4)	4 (4·0)
Permanent treatment discontinuation due to TEAE	10 (4·5)	16 (13·4)	4 (4·0)
Death	0	1 (0·8)	0
Injection-site reaction TEAEs[b]	37 (16·7)	21 (17·6)	25 (24·8)
Hypersensitivity TEAEs[c]	10 (4·5)	4 (3·4)	6 (5·9)

What does this study add?

- This phase III study confirmed equivalent efficacy for MSB11022 and reference adalimumab in patients without any immunomodulation comedication in moderate-to-severe chronic plaque-type psoriasis at week 16.
- The efficacy, safety and immunogenicity of MSB11022 and reference adalimumab were similar over the respective observation periods (week 52 for efficacy and immunogenicity, week 66 for safety).
- A switch from reference adalimumab to MSB11022 at week 16 did not impact efficacy, safety or immunogenicity.

Clinical Rheumatology
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ORIGINAL ARTICLE

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

Christopher J. Edwards[1] · Joëlle Monnet[2] · Martin Ullmann[2] · Pantelis Vlachos[3] · Veranika Chyrok[2] · Vishal Ghori[2]

AURIEL-RA study was a phase 3, multicenter, randomized, double-blind, parallel group trial (NCT03052322)

Στόχος

Να συγκριθεί

- η ασφάλεια,
- η αποτελεσματικότητα &
- η ανοσογονικότητα του MSB11022 (βιομοειδούς του adalimumab, με το προϊόν αναφοράς)

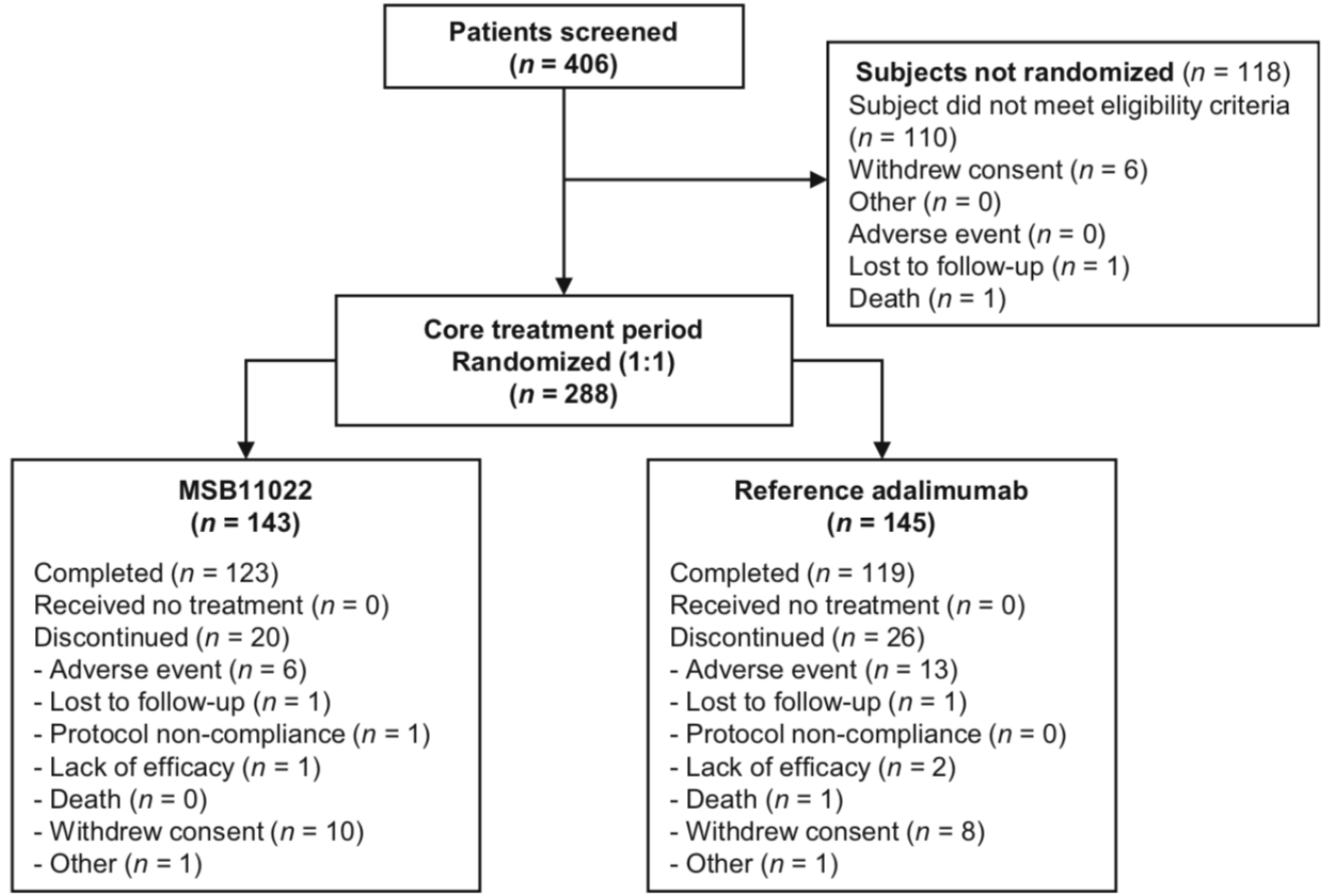
Method AURIEL-RA study was a phase 3, multicenter, randomized, double-blind, parallel group trial (NCT03052322). Patients with moderately-to-severely active rheumatoid arthritis (RA) with an inadequate response to methotrexate were randomized 1:1 to MSB11022 or reference adalimumab. The primary endpoint was the incidence of treatment-emergent adverse events of special interest (AESIs) (predefined as hypersensitivity) up to week 52. The key secondary endpoint was ACR20 ($\geq$ 20% improvement in American College of Rheumatology core set measurements from baseline) at week 12. Other efficacy endpoints, quality of life, immunogenicity, and pharmacokinetic parameters were evaluated up to week 52. Secondary safety endpoints were evaluated up to week 52 and at a 4-month safety follow-up.

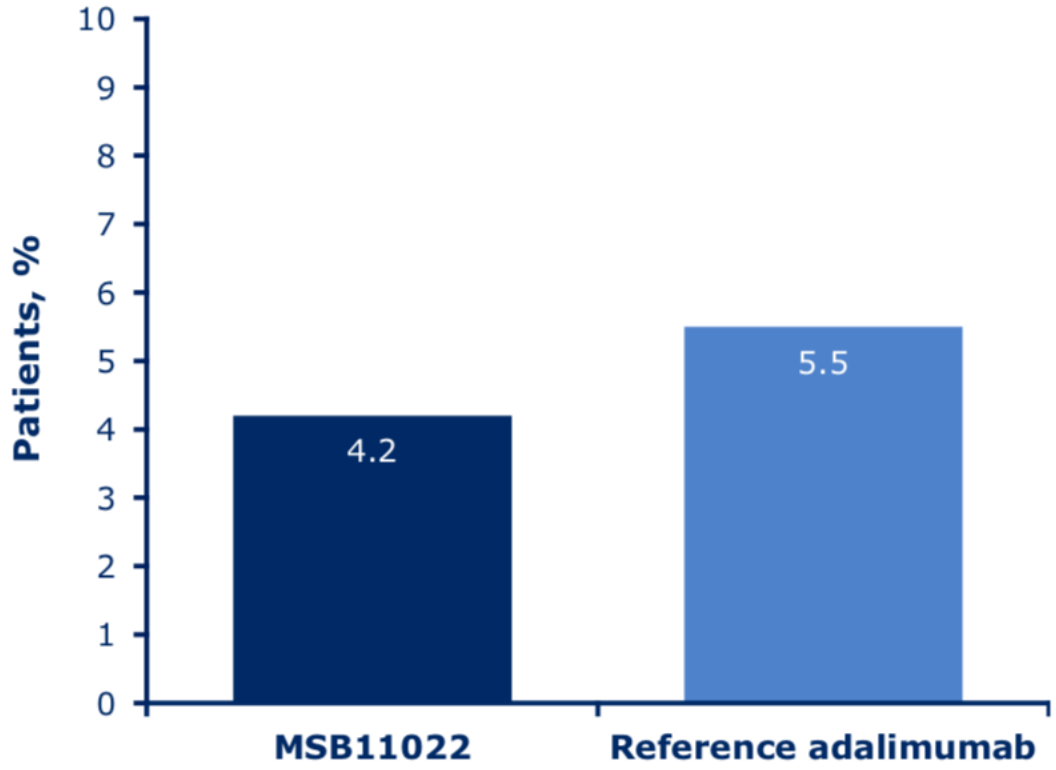
Table 1 Baseline demographic and clinical characteristics (ITT analysis set)

	MSB11022 ($n = 143$)	Reference adalimumab ($n = 145$)
Male, *n* (%)	35 (24.5)	26 (17.9)
Age (years), mean (SD)	53.9 (12.0)	54.0 (11.0)
Race, *n* (%)		
Caucasian	142 (99.3)	143 (98.6)
Black	0	0
Asian	0	2 (1.4)
American Indian or Alaska Native	0	0
Native Hawaiian/Other Pacific Islander	0	0
Other	1 (0.7)	0
Body mass index (kg/m^2), mean (SD)	27.3 (4.7)	27.0 (5.1)
Patient's Global Assessment of Disease Activity, mean (SD) (median [range])	6.8 (1.5) (7.0 [1.0–10.0])	6.9 (1.6) (7.0 [1.5–10.0])
Physician's Global Assessment of Disease Activity, mean (SD) (median [range])	6.8 (1.2) (7.0 [3.5–9.5])	6.7 (1.2) (7.0 [3.5–9.0])
Patient assessment of arthritis pain, mean (SD) (median [range])	6.7 (1.5) (6.9 [2.8–10.0])	6.7 (1.8) (6.9 [0.3–10.0])
HAQ-DI, mean (SD) (median [range])	1.6 (0.6) (1.6 [0–2.6])	1.6 (0.6) (1.8 [0–2.9])
Tender joint count, mean (SD) (median [range])	23.3 (12.0) (21.0 [7–66])	22.0 (9.9) (21.0 [7–56])
Swollen joint count, mean (SD) (median [range])	13.8 (6.9) (12.0 [6–40])	12.6 (5.4) (12.0 [6–38])
C-Reactive protein (mg/l), mean (SD) (median [range])	1.1 (1.8) (0.60 [0.1–13.7])	1.3 (2.0) (0.60 [0.0–11.6])
DAS28-ESR, mean (SD) (median [range])	5.7 (0.7) (5.7 [3.7–7.2])	5.5 (0.8) (5.5 [2.3–7.5])
CDAI, mean (SD) (median [range])	39.4 (11.0) (38.4 [14.0–65.2])	36.6 (10.0) (34.8 [14.4–67.7])
SDAI, mean (SD) (median [range])	40.5 (11.2) (39.2 [15.8–73.6])	37.9 (10.5) (35.9 [16.3–69.9])
Previous systemic biologic, *n* (%)	14 (9.8)	16 (11.0)
Previous biologic or other immunosuppressants, *n* (%)		
Etanercept	9 (6.3)	10 (6.9)
Infliximab	1 (0.7)	3 (2.1)
Overall	45 (31.5)	60 (41.4)

ACR American College of Rheumatology, *CDAI* Clinical Disease Activity Index, *DAS28-ESR* Disease Activity Score 28-joint erythrocyte sedimentation rate, *HAQ-DI* Health Assessment Questionnaire for Rheumatoid Arthritis, *SD* standard deviation, *SDAI* Simple Disease Activity Index

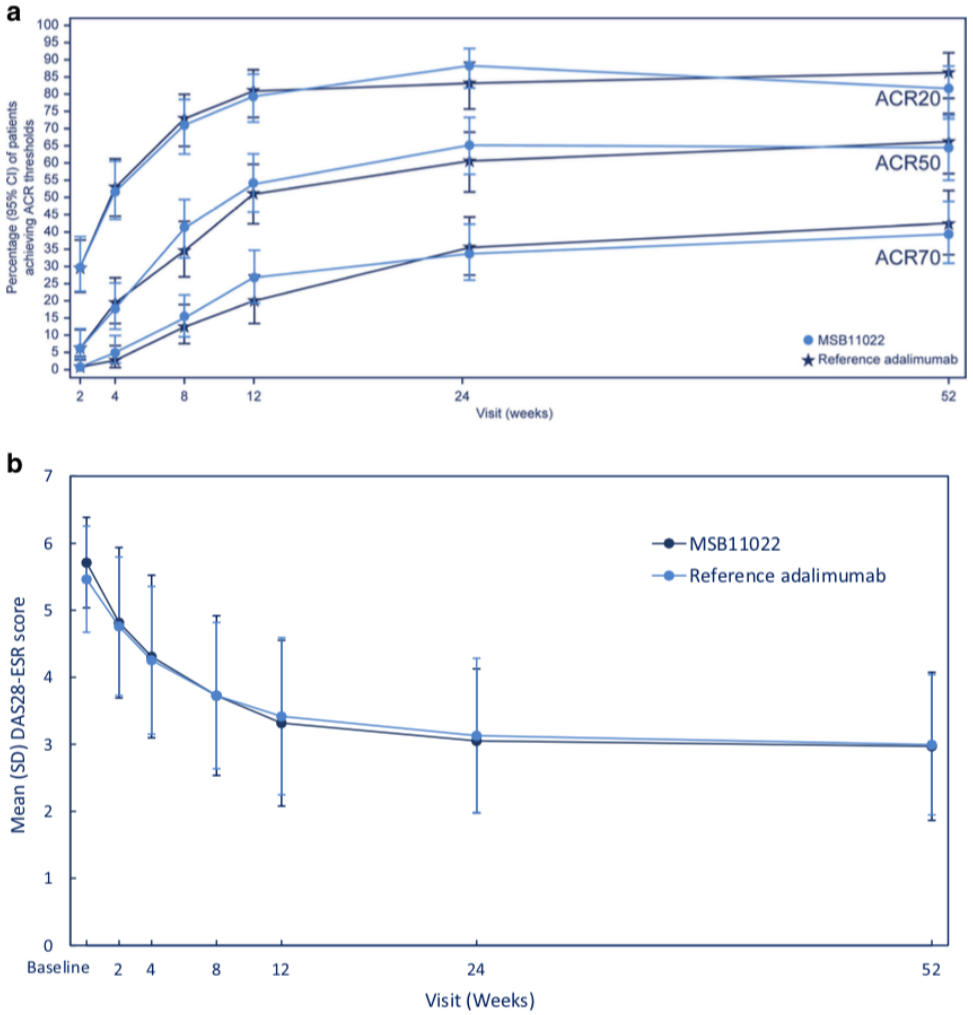
Fig. 1 Patient disposition



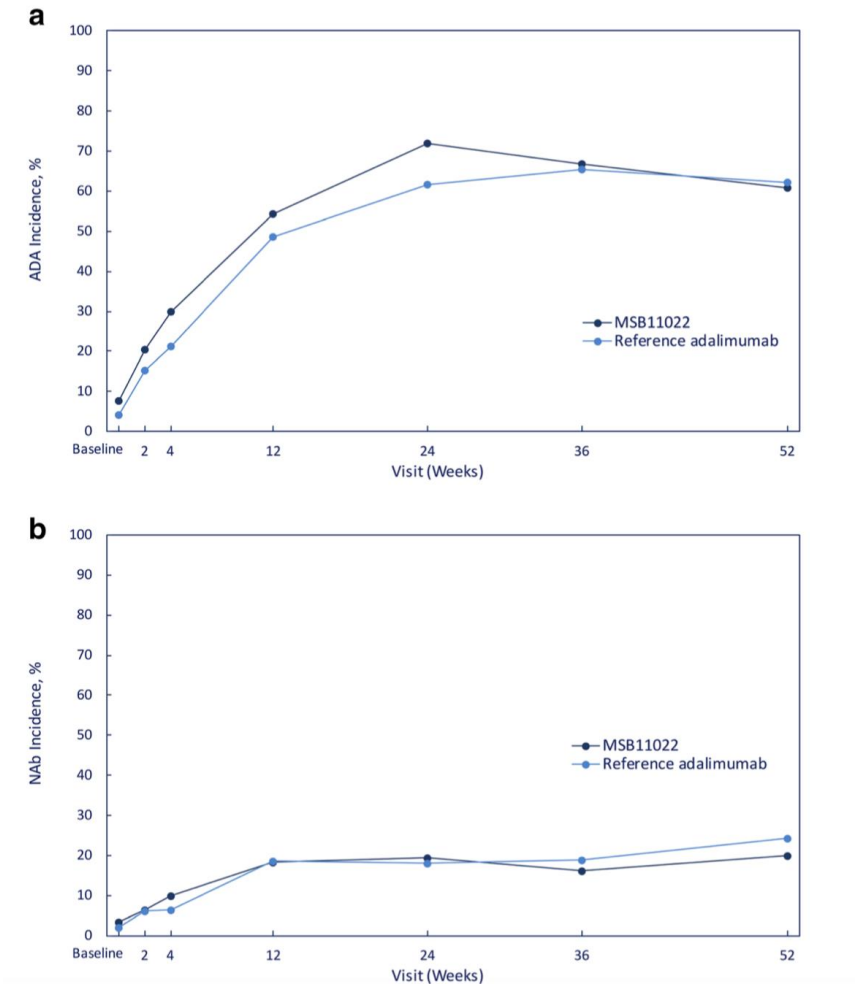


Patients	6	8
95% CI	1.56, 8.91	2.41, 10.58
Events	7	8

Fig. 2 Primary endpoint: Proportion of patients with AESIs of hypersensitivity by treatment arm (safety analysis set). AESI, adverse event of special interest



Secondary endpoint: ACR20/50/70 response (a) and mean (SD) DAS28-ESR score (b) by study week (ITT analysis set).



Incidence of antidrug antibodies (a) and neutralizing antibodies (b) from baseline to week 52 (safety analysis set). ADA, antidrug antibody; NAb, neutralizing antibody

Table 2 Treatment-emergent adverse events up to weeks 52 and during the 4-month safety follow-up (safety analysis set)

	Double-blind treatment period		4-month safety follow-up	
n (%) patients	MSB11022 (*n* = 143)	Reference adalimumab (*n* = 145)	MSB11022 (*n* = 143)	Reference adalimumab (*n* = 145)
TEAE	83 (58.0)	93 (64.1)	6 (4.2)	6 (4.1)
Serious TEAE	7 (4.9)	14 (9.7)	2 (1.4)	1 (0.7)
Treatment-related TEAE	31 (21.7)	58 (40.0)	0	0
Serious treatment-related TEAE	1 (0.7)	3 (2.1)	0	0
Permanent treatment discontinuation due to TEAE	6 (4.2)	14 (9.7)	NA	NA
Death	0	1 (0.7)	0	1 (0.7)
TEAE of special interest (hypersensitivity)	6 (4.2)	8 (5.5)	NA	NA
Dermatitis allergic	1 (0.7)	2 (1.4)		
Rash	2 (1.4)	1 (0.7)		
Urticaria	1 (0.7)	2 (1.4)		
Dermatitis	0	2 (1.4)		
Anaphylactic reaction	1 (0.7)	0		
Drug hypersensitivity	1 (0.7)	0		
Injection site urticaria	0	1 (0.7)		
Rash vesicular	1 (0.7)	0		

NA not applicable, *TEAE* treatment-emergent adverse event

Βασικά Σημεία

- Τα περιστατικά συμβάντων υπερευαισθησίας ήταν παρόμοια για το MSB11022 (τροποποιημένο buffer) και το adalimumab αναφοράς
- Δεν υπήρχε διαφορά στις τοπικές αντιδράσεις μεταξύ του MSB11022 (τροποποιημένο ρυθμιστικό διάλυμα) και του adalimumab προιόντος αναφοράς
- Η AURIEL-RA επιβεβαιώνει την ισοδυναμία αποτελεσματικότητας και ανοσογονικότητας του MSB11022 και του adalimumab αναφοράς