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Treat-to-target strategy with secukinumab as a first-line biological disease modifying anti-rheumatic drug compared to standard-of-care treatment in patients with active axial spondyloarthritis: protocol for a randomised open-label phase III study, AScalate

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ABSTRACT

Introduction In patients with axial spondyloarthritis (axSpA), biological disease-modifying anti-rheumatic drugs (bDMARDs) are recommended to those with inadequate response or contraindications to non-steroidal anti-inflammatory drugs (NSAIDs). In case of failure of the first bDMARD, a switch within the class or to other bDMARD is recommended. Despite these treatment options, there is no optimal treat-to-target (T2T) strategy. This study aims to evaluate the efficacy of a T2T strategy in patients with axSpA, with secukinumab as a first-line bDMARD, compared with standard-of-care (SOC) treatment.

Methods and analyses This is a randomised, parallel-group, open-label, multicentre ongoing study in patients with axSpA who are naïve to bDMARD and who have had an inadequate response to NSAIDs. The study will include an 8-week screening period, a 36-week treatment period and a 20-week safety follow-up period. At baseline, patients will be randomised (1:1) to T2T or SOC group. In the T2T group, patients will be treated with secukinumab 150 mg subcutaneous (s.c.) weekly until week 4 and then at week 8. For non-responders (patients without Ankylosing Spondylitis Disease Activity Score [ASDAS] clinically important improvement; change from baseline ≥1.1) at week 12, dose will be escalated to 300 mg s.c. every 4 weeks until week 24. Non-responders at week 24 will be switched to adalimumab biosimilar 40 mg s.c. every 2 weeks until week 34. In the SOC group, patients will receive treatment at the discretion of the physician. The primary endpoint is the proportion of patients achieving an Assessment in SpondyloArthritis International Society 40% (ASAS40) response at week 24.

Ethics and dissemination The study is being conducted as per the ethical principles of the Declaration of Helsinki and after approval from independent ethics committees/institutional review boards. The first results are expected to be published in early 2022.

Strengths and limitations of this study

- This is the first randomised controlled study to compare the efficacy of secukinumab as a first-line biological disease-modifying anti-rheumatic drug versus standard-of-care (SOC) treatment to provide an evidence-based optimal treatment strategy for patients with axial spondyloarthritis (axSpA) who are naïve to biological therapy and who have had an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs).
- To date, this is one of the few studies to use a treat-to-target (T2T) approach in axSpA.
- This study design is simple and representative of routine clinical practice.
- A potential limitation of this study could be its open-label design, which might challenge the internal validity of reported results.
- Another limitation is related to a potential impact of the T2T approach on the treatment of patients in the SOC group.

Trial registration number This study is registered with ClinicalTrials.gov, NCT03906136.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disorder that primarily affects the sacroiliac joints and spine. Based on the absence or presence of sacroiliitis on conventional radiographs, axSpA can be classified into two subtypes: non-radiographic axSpA (nr-axSpA) and ankylosing spondylitis (AS) or radiographic

axSpA.[1 2] Both axSpA subtypes, nr-axSpA and AS, have generally similar clinical characteristics, and about 12% of the patients with nr-axSpA progress to AS over 2 years.[2–4]

The diagnosis of axSpA is often delayed by 6–9 years, usually because of late referral to a rheumatologist.[5 6] Short symptom duration is, however, one of the best predictors of treatment response in axSpA.[7 8]

For axSpA, non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment, followed by treatment with biological disease-modifying anti-rheumatic drugs (bDMARDs) in patients who do not respond to NSAIDs or have contraindications to NSAIDs.[9 10] In case of failure of the first bDMARD, a switch within the class or between classes of other bDMARDs such as tumour necrosis factor-alpha inhibitors (TNFi) is recommended, but there is not enough evidence to support either strategy.[9 10] The 2016 updated Ankylosing SpondyloArthritis International Society (ASAS)/European League Against Rheumatism recommendations suggest to start bDMARD therapy with a TNFi. However, if a patient with axSpA has inadequate response or becomes intolerant to TNFi therapy, anti-interleukin-17A (IL-17A) agents can be considered for the treatment of axSpA.[9–11]

Secukinumab, a human monoclonal IgG1κ antibody that directly inhibits IL-17A, demonstrated rapid and long-lasting reduction in the signs and symptoms of active AS in two pivotal phase III studies (MEASURE 1: NCT01358175 and MEASURE 2: NCT01649375).[12–15] Clinical efficacy of secukinumab was evident in patients with AS who were either bDMARD naïve or had a history of treatment with TNFi.[12–15] bDMARDs have improved the treatment outcomes and quality of life (QoL) of patients with axSpA, and also brought about a change in the treatment goal towards remission or low disease activity, as mentioned in recent treat-to-target (T2T) recommendations.[10 16 17] Despite these therapeutic options for axSpA, many questions related to the optimal treatment strategy for T2T approach remain unanswered, such as: What is the optimal first bDMARD in axSpA? Could dosage escalation of an IL-17A blocker in patients not reaching the newly defined treatment target lead to achievement of the treatment goal? Would a TNFi after IL-17A inhibitor treatment be beneficial to patients? This randomised controlled study (AScalate) is being conducted in order to answer these questions.

METHODS AND ANALYSIS

Aim

The aim of this study is to demonstrate the efficacy of a T2T treatment strategy, with secukinumab as a first-line bDMARD, compared with standard-of-care (SOC)[11] treatment over 36 weeks in patients with active axSpA who arenaïve to bDMARDs and who have had an inadequate response to NSAIDs.

Study design

This is a randomised, parallel-group, open-label, multicentre study in patients with active axSpA (defined as Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥2.1 at screening and at baseline despite concurrent NSAID therapy, or intolerance/contraindication to NSAIDs). The study will include an 8-week screening period, a 36-week treatment period and a safety follow-up period of 20 weeks. Patients will be evaluated every 12 weeks from baseline up to week 36. At baseline, patients will be randomised (1:1) to T2T or SOC group (figure 1). At the randomisation visit, the investigator will assign each patient to the lowest available randomisation number as per the corresponding sealed treatment allocation card. A randomisation list will be produced by or under the responsibility of Novartis Biometrics Department using a validated system that automates the random assignment of treatment groups to randomisation numbers in the specified 1:1 ratio. The randomisation scheme will be reviewed and locked after approval. According to the recommendations given in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E9 Guideline 'Statistical Principles for Clinical Trials', the used block length is specified in a separate document, which will be with-held from the study centres.

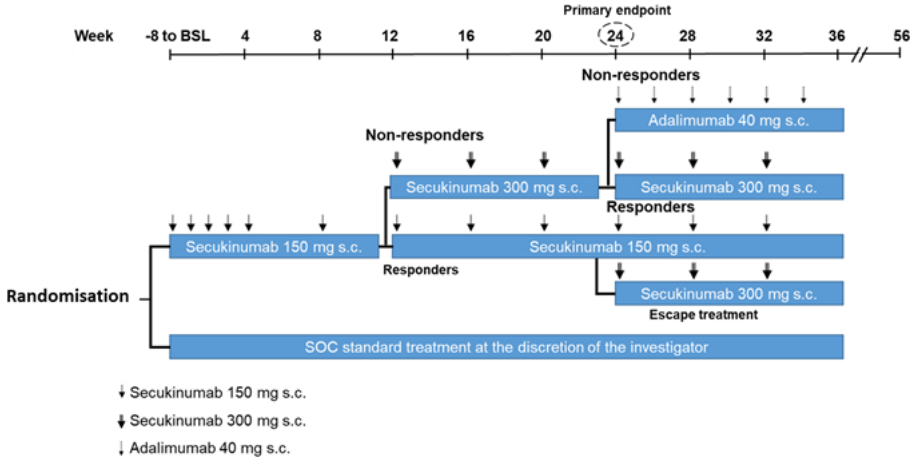

Figure 1 Study design. BSL, baseline; s.c., subcutaneous;SOC, standard-of-care .

In the T2T group, all patients will be treated with secukinumab 150 mg subcutaneous (s.c.) from baseline to weeks 1, 2, 3, 4 and then every 4 weeks (q4w) starting at week 8. At week 12, responders (patients with ASDAS clinically important improvement, defined as change from baseline ≥1.1) will continue q4w dosing until week 32 if they maintain the response. For non-responders at week 12, dose will be escalated to 300 mg s.c. q4w until week 20. Responders at week 24 will continue receiving secukinumab 300 mg s.c. q4w up to week 32. However, non-responders at week 24 will be switched to adalimumab biosimilar 40 mg s.c. every 2 weeks (q2w) until week 34. Furthermore, patients who were responders at week 12 but experienced a loss of response (defined as ASDAS change from baseline <1.1) at week 24 will be switched to an escape treatment and treated with secukinumab 300 mg s.c. q4w through to week 32. In the SOC group, patients will receive treatment at the discretion of the physician in accordance with local practice standards, following the current treatment recommendations with NSAIDs as the first-line treatment and bDMARDs for patients with active disease despite the use (or intolerance/contraindication) of NSAIDs.[10]

Safety evaluations will be included in the regular visits and a follow-up visit will be performed 20 weeks after the last visit (ie, week 36) and will take place at week 56 for patients completing the study according to the protocol. In addition, patients in the T2T arm will be monitored for safety at weeks 4 and 8. Patients who prematurely discontinue completely from the study for any reason should return to complete the weeks 36 and 56 assessments.

This protocol is described using the 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines on standard protocol items for clinical trials.[18]

Patient involvement

Patients were involved in the design and conduct of this research. During the feasibility stage, priority of the research question, choice of outcome measures and methods of recruitment were informed by discussions with patients through a focus group session. During the trial, a patient from the German ankylosing spondylitis association 'Deutsche Vereinigung Morbus Bechterew e.V.' joined the independent trial steering committee. At the end of the study participation, each patient will receive a 'Thank you letter' containing a link to a dedicated website (novartisclinicaltrials.com). Once the trial has been published, participants will find Plain Language Trial Summaries of the study results on this website.

Patient population

A total of 300 patients of either sex, ≥18 years of age, who meet all of the following criteria will be included: (1) confirmed diagnosis of axSpA (either nr-axSpA or AS) fulfilling the ASAS classification criteria for axSpA[1]; (2) active disease as defined by having an ASDAS ≥2.1 at screening and at baseline despite concurrent NSAID therapy, or intolerance/contraindication to NSAIDs; (3) objective signs of inflammation at screening, as defined by magnetic resonance imaging (MRI) of sacroiliac joints and spine performed during screening period or up to 3 months prior to screening showing acute inflammatory lesion(s) or elevated quick C-reactive protein (CRP; >5 mg/L); (4) patients should have been on at least two different NSAIDs at the highest recommended dose for at least 4 weeks in the past, with an inadequate response or failure to respond, or less if therapy had to be reduced due to intolerance, toxicity or contraindications (NSAIDs inadequate responder); (5) those regularly taking NSAIDs as part of therapy are required to be on a stable dose for at least 1 week before randomisation; (6) patients taking methotrexate (7.5–25 mg/week) or sulfasalazine (≤3 g/day) are allowed to continue their medication but are required to be on a stable dose for at least 4 weeks before randomisation; (7) patients who are on a DMARD other than methotrexate or sulfasalazine must discontinue the DMARD 4 weeks prior to randomisation; (8) patients taking corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomisation and should remain on a stable dose up to week 24. Key exclusion criteria are shown in box 1.

Box 1 Key exclusion criteria

- Patients with a previous exposure to secukinumab or other interleukin 17 inhibitor, tumour necrosis factor inhibitor or any investigational agents (4 weeks or ≤5 half-lives of the drug prior to baseline).
- Patients with active ongoing inflammatory (other than axial spondyloarthritis) or infectious diseases or underlying metabolic disorders that could be a risk for receiving an immunomodulatory therapy.
- Active systemic infections during the last 2 weeks prior to randomisation or history or evidence of tuberculosis infection.
- Patients positive for HIV, hepatitis B or C at randomisation.
- Pregnant or nursing (lactating) women.
- Patients with a history of lymphoproliferative disease or any known malignancy (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
- Live vaccinations within 6 weeks prior to baseline.

Endpoints

The primary endpoint is the proportion of patients achieving an Assessment in SpondyloArthritis International Society 40% (ASAS40) response at week 24.

Secondary endpoints are the proportion of patients achieving (1) an ASAS40 response at week 12; (2) an ASDAS[19] clinically important improvement (defined as change from baseline of ≥1.1) at weeks 12 and 24; (3) ASDAS <2.1 (low disease activity)[20] at weeks 12 and 24; (4) ASAS20 at weeks 12 and 24; (5) ASAS partial remission (PR) at weeks 12 and 24; and (6) Bath Ankylosing Spondylitis Disease Activity Index 50% (BASDAI50) at weeks 12 and 24. Furthermore, the efficacy of a T2T approach over SOC treatment will also be evaluated in terms of

improvement of disease activity, function, axial mobility and QoL measures at weeks 12 and 24 as compared with baseline according to: BASDAI, ASDAS, high-sensitivity (hs) CRP and erythrocyte sedimentation rate (ESR), Bath Ankylosing Spondylitis Functional Index (BASFI),[21] Bath Ankylosing Spondylitis Metrology Index (BASMI)[22] and chest expansion, global assessment of disease activity (patient/physician) and general pain on Visual Analogue Scale (VAS),[23] ASAS Health Index (ASAS-HI),[24] 36-Item Short Form Survey (SF-36),[25] Ankylosing Spondylitis Quality of Life (ASQoL)[26] and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue).[27] Additional secondary endpoints are safety and tolerability of secukinumab.

The exploratory endpoints are to assess the efficacy of T2T versus SOC approach at week 36 of the following: ASAS40, ASDAS clinical improvement, ASDAS <1.3, ASDAS <2.1, ASAS20, ASAS PR and BASDAI50 responses at week 36 (box 2). In addition, improvement in peripheral involvement and enthesitis will be assessed, compared with baseline, at weeks 12, 24 and 36; and disease activity, function, axial mobility and QoL measures will be assessed at week 36 compared with baseline (box 2).

Box 2 Exploratory endpoints

- At week 36, proportion of patients achieving:
  - An ASAS40 response
  - An ASDAS clinically important improvement
  - ASDAS <1.3
  - ASDAS <2.1
  - ASAS20, ASAS PR, BASDAI50 responses
- At weeks 12, 24 and 36 versus baseline, improvement in:
  - Peripheral involvement (44 TJC/ SJC)
  - Enthesitis (MASES)
- At week 36 versus baseline, improvement of disease activity, function, axial mobility and QoL measures according to:
  - BASDAI
  - ASDAS
  - hsCRP and ESR
  - BASFI
  - BASMI and chest expansion
  - Global assessment of disease activity (patient/physician)
  - General pain on the VAS, ASAS-HI, SF-36, ASQoL, FACIT-Fatigue
- Correlation of baseline hsCRP or MRI assessment of sacroiliac joints or spine with treatment response
- Exploratory pharmacogenetic assessments to examine whether individual genetic variation in genes relating to the indication and the drug target pathway confer differential responses
- Comparison of the proportion of responders between the secukinumab T2T patients and the SOC patients specifically treated according to the recommended treatment algorithm
- At week 36, proportion of patients achieving:
  - An ASAS40 response
  - An ASDAS clinically important improvement
  - ASDAS <1.3
  - ASDAS <2.1
  - ASAS20, ASAS PR, BASDAI50 responses

ASAS PR, Ankylosing Spondyloarthritis International Society Partial Remission; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index 50%; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; ESR, erythrocyte sedimentation rate; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; HI, Health Index; hsCRP, high-sensitivity C reactive protein; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; SF-36, 36-Item Short Form Survey; SJC, swollen joint count; SOC, standard of care; T2T, treat-to-target; TJC, tender joint count; VAS, Visual Analogue Scale.

Site monitoring and data management

Data will be collected electronically using the electronic case report forms (eCRFs). Sponsor or designated contract research organisation will review the data entered by investigational staff for completeness and accuracy. To enhance validity of data, multiple methods will be used to assess treatment adherence including patient diary, manual entry of the actual date of injection by site staff and a remote centralised electronic monitoring system. Automatic validation programmes check for data discrepancies in the eCRFs will allow modification and/or verification of the entered data by the investigator staff. Any changes to the database, once it will be locked, can only be made after written agreement by Novartis development management. Furthermore, any modification to the protocol can only be made in a written protocol amendment that must be approved by sponsor, health authorities where required and the institutional review board (IRB)/independent ethics committee (IEC) prior to implementation.

Audits of investigator sites, vendors and sponsor systems will be performed according to written sponsor processes, by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial.

Sample size calculations

An interim analysis following the approach proposed by Bauer and Köhne[28] will be performed to evaluate the assumptions of the sample size calculation and possibly adapt the sample size according to the outcome of the interim analysis. The two-stage design allows through the interim analysis, which will be performed after 75 patients per group complete the assessment of the primary endpoint variable at 24 weeks of treatment, to possibly adapt the planned sample size. To keep the global type I error rate at 2.5% (one-sided, equivalent to 5%; two-sided), the critical limits will be $\alpha 1=0.00380$, $\alpha 0=1$ and $c\alpha=0.00380$[28]; that is, the null hypothesis will be rejected after the second part of the study, if the product of p1 and p2 does not exceed $c\alpha$, with p1 and p2 being the p value from the interim analysis and the second part of the study, respectively. The study will be completed successfully (ie, with rejection of the null hypothesis) after the interim analysis, if the p value for the primary comparison will be <0.00380.

The sample size will be calculated based on the primary endpoint, ASAS40 response at week 24. Data from

previous studies showed an ASAS40 response of 30.0% and 43.0% in patients with axSpA treated with bDMARDs and secukinumab, respectively.[29–32] Taking into account the longer duration of treatment with secukinumab 150 mg and the substantial proportion of patients that will be escalated to 300 mg, it is justifiable to conservatively assume an ASAS40 response of 50% at week 24. With an ASAS40 response of 50% for the secukinumab 150 or 300 mg arm and a 30% response in the SOC arm at week 24, 134 patients per treatment arm will be required to achieve a power of 90% to demonstrate superiority at a significance level of 0.05 using the two-group continuity corrected χ^2 test of equal proportions. Considering some uncertainties in the underlying assumptions and some expected dropout and protocol violations, 300 patients will be recruited.

Statistical analyses

The analyses will be conducted on all patient data after database lock for the trial. The primary and secondary analyses will be carried out after the last patient has completed week 24 assessment. As the study continues into an exploratory phase until week 36, no formal adjustment of type I error is required. The primary analysis will be performed comparing treatments with respect to the primary endpoint in a multiple logistic regression model with treatment and centre as factors, and weight as well as baseline hsCRP level as covariates. A multiple logistic regression model will be applied for other binary variables, with treatment and centre as factors, and baseline score if appropriate (only ASDAS and BASDAI50 will have their baseline value) and weight as covariates. The odds ratio (OR), 95% confidence interval (CI) and p value will be given. The null hypothesis of equal odds will be rejected if the two-sided p value from the logistic regression model for the factor 'treatment' is <0.05.

Patients without a valid ASAS40 assessment at week 24 will be regarded as non-responders for the primary analysis (non-responder imputation; NRI). NRI will also be applied to all secondary response variables.

Mean changes from baseline in the ASDAS, BASDAI, BASFI, BASMI and chest expansion, PGA, ASDAS-CRP/ESR, total joint count, swollen joint count, Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and health-related QoL secondary and exploratory endpoints (SF-36 physical and mental component scores, ASQoL, ASAS-HI) will be analysed using a mixed-effect model for repeated measures (MMRM) through weeks 12, 24 and 36 with treatment regimen and analysis visit as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score as interaction terms. An unstructured covariance structure will be assumed.

The safety analysis will include all patients who received at least one dose of study drug or reference treatment. Coding of adverse events will be done using the Medical Dictionary for Regulatory Activities (V.23.0). Safety data will be summarised descriptively. All endpoints relating to exploratory objectives from week 24 onwards until end of study will be summarised descriptively.

Study discontinuation and compensation for researchrelated injuries

A patient may discontinue the study for any reason at any time. However, these patients will not be considered withdrawn from the study unless they withdraw their consent. If these patients fail to return for the scheduled assessments for unknown reasons, they can be contacted through telephone, email or letter to retain a patient in the study. No further data will be collected after withdrawal of consent but previously collected data could be included in the analysis. The investigator also may withdraw patients from the study to protect their safety. The study can be terminated by sponsor at any time for any reason.

Sponsor will cover the reasonable costs of treatment for research related injuries under the following conditions and in accordance with local laws: (1) if a patient received medical care and followed instructions; (2) if the injury is related to properly performed sample collection procedures that are not part of a patient's usual medical care; (3) if the injury is not the result of the natural course of any disease existing before collection of sample(s).

Ethics and dissemination

The study will be conducted as per the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines and local regulations and after approval from an IRB/IEC in each centre; list of ethical approval reference numbers for each participating centre has been provided in online supplemental table 1. All patients are required to provide written informed consent to the investigator. A separate consent form will be signed by patients for pharmacogenetic testing.

The study has been started in June 2019 by achieving the first patient first visit on 3 June 2019. Around 50 sites in Germany and France have been involved into this study. The first results are expected to be available in early 2022. The results of the entire study (data of week 56) will be published approximately 1 year later.

The study is registered in EudraCT registry (registration number 2018-003882-32) and at ClinicalTrials.gov (registration number NCT03906136).

DISCUSSION

Currently, there is not enough evidence to support the use of a particular class of bDMARD or switch within class or between classes in case of the failure of the first bDMARD in patients with active axSpA who have had an inadequate response to NSAID therapy.[9 10] The study is expected to throw light on a clinically pertinent question: whether a T2T approach with secukinumab as first-line bDMARD results in superior efficacy compared with the SOC treatment in patients with active axSpA who have had an inadequate response to NSAID therapy. The findings should

help to elucidate an optimal treatment strategy for this patient population.

Adalimumab has been selected as the second bDMARD for the T2T approach (in case of insufficient response to secukinumab treatment at week 24) as this is a commonly used TNFi, approved for the treatment of patients with AS or nr-axSpA, and which confers similar efficacy to secukinumab in terms of signs and symptoms.[33]

This study design is simple and easy to understand because it is closely related to clinical practice.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

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