Statistical analysis plan

The Use of Steovess/Binosto After Denosumab Discontinuation to Prevent Increase in Bone Turnover

NCT04403698
EudraCT number: 2019-003570-11
Protocolnumber: BC-6072

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Version 2

Content

1. Study identification

1.1 Study details

Title: The use of buffered soluble alendronate 70 mg (Steovess/Binosto) after denosumab discontinuation to prevent increase in bone turnover

Trial registration number: EudraCTNr: 2019-003570-11
EC approval number: BC-6072
Principal investigators: Ruth Wittoek
Subinvestigators: Dirk Elewaut, Tine Vanhaverbeke
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1.2 SAP details

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2. Background and rationale of the study

2.1 Background

Denosumab, anti-RANK ligand therapy discontinuation, is associated with a rebound in bone turnover and loss of bone mineral density. These changes result in increased fracture incidence in patients with postmenopausal osteoporosis back to background levels. Amongst the patients that presented with vertebral fractures after treatment discontinuation, there is a slightly higher incidence of multiple vertebral fractures in patients discontinuing Prolia versus those that discontinued placebo.

In our study 'RANKL-blockade for the treatment of erosive hand osteoarthritis (OA) of interphalangeal finger joints' (EudraCT number: 2015-003223-53; Protocolnumber: AGO/2015/008) patients are randomized to placebo or denosumab (60 mg/Q3M) for 1 year followed by a two-year open label extension in which all subjects receive denosumab (60 mg/Q3M) (1). Also in this non-osteoporotic population, increases in bone turnover are expected as soon as patients end study participation.

It is currently recommended that other anti-resorptive therapy may is warranted after Denosumab discontinuation. Several studies describe the use of oral alendronate after denosumab therapy to maintain bone mineral density. However, gastro-intestinal upset and tolerability, as well as difficulty swallowing pills may limit oral alendronate use. In the current study proposal we want to examine the use of effervescent alendronate (Steovess/Binosto) in subjects that completed our hand erosive osteoarthritis study and therefore discontinued denosumab 60 mg/Q3M.We hypothesize that Steovess/Binosto will be able to maintain bone turnover markers within the reference range thereby reducing the likelihood of bone turnover associated changes.

In erosive hand OA, destructive erosive changes, followed by remodelling is key characteristic for the disease. As in inflammatory rheumatic diseases, the RANKL pathway appears to be involved in the pathogenesis and hence, a therapeutic role of its blockade has been studied in the study described above. It is unknown if a potential rebound effect in bone turnover might also be associated with a rebound in erosive destructive progression at the subchondral bone.

2.2 Hypothesis and objectives

It is hypothesized that effervescent alendronate will be able to maintain bone turnover markers within the reference range thereby reducing the likelihood of bone turnover associated changes, after discontinuation of denosumab treatment in a non-osteoporotic population.

The **primary objective** of this study is to assess the effect of effervescent alendronate after denosumab discontinuation on the change in bone turnover markers after 48 weeks in a non-osteoporotic population and to assess if there is a difference between using oral alendronate after 24 or 48 weeks.

The **secondary objective** is to evaluate the effect of effervescent alendronate after denosumab discontinuation on bone mineral density in this non-osteoporotic population and assess difference in oral alendronate therapy for 24 versus 48 weeks.

Exploratory objectives are to study the effect of oral alendronate therapy after denosumab discontinuation on erosive destructive progression at the subchondral bone in erosive hand OA patients and to assess the effect of oral alendronate on their hand pain scores.

2.3 Study design

This is a monocentric randomized study to investigate the effect of effervescent alendronate on bone turnover markers after denosumab discontinuation. At the earliest three months but no later than

four months after the last denosumab injection, 40 subjects will be randomized to effervescent alendronate administered for either 24 (n=20) or 48 weeks (n=20). The randomization was performed by a randomization manager. The total treatment duration per subject is 48 weeks.

3. Study population

3.1 Inclusion and exclusion criteria

Cfr Protocol (version 1.0 dd 09/08/2019)

3.1.1. Inclusion criteria

A subject will be eligible for study participation if he/she meets the following criteria:

- Subjects must have completed the 48 weeks of the randomised placebo-controlled study phase followed by the 96 weeks open label denosumab 60 mg SC every 3 months phase. (EudraCT number: 2015-003223-53)
- Last denosumab injection less than four months ago
- Able and willing to give written informed consent and to comply with the requirements of the study protocol

3.1.2 Exclusion criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

- Patients with clinically significant hypersensitivity to any of the components of effervescent alendronate.
- Patient who is pregnant or planning pregnancy
- Female subjects who are breast-feeding.
- History of osteonecrosis of the jaw, and/or recent (within 3 months) tooth extraction or other unhealed dental surgery; or planned invasive dental work during the study
- Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures
- Hypocalcaemia.
- Oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty.
- Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.

3.2 Data sets analysed

3.2.1 Safety analysis

The safety dataset includes all patients who received at least 1 dose of effervescent alendronate. This dataset will be used to summarize adverse events and safety analysis.

3.2.2 Full analysis dataset

The full analysis set will include all patients who are randomly allocated to a treatment group and received at least 1 dose of effervescent alendronate.

3.2.3 Protocol violations and handling of missing data

Major protocol violations thought to affect the assessment of efficacy of the study drug will be considered. The following situations will be considered as major protocol violations:

- Patients who withdrew or were withdrawn from the study
- Patients having received less than 50% of the study medication

Data of withdrawn patients will be included up until the moment of withdrawal. If measurements are recorded after withdrawal when not completed the appropriate duration of active treatment, these measurements will be considered as missing. For analysis of the primary endpoint, all data available will be used for analysis and imputation of missing values will be performed. More specifically, drop-outs will be considered as non-responders in all outcome measures (primary and secondary endpoints where linear mixed models will be used, and in the number of patients exceeding reference ranges). Only in the analyses of percentage changes of BMD and percentage of patients with a BMD loss higher than the least significant change, drop-outs will be considered as true drop-outs.

4. Outcome measures

4.1 Primary endpoints

The primary end point of this study is to investigate if effervescent alendronate is able to maintain bone turnover markers after discontinuation of denosumab in a non-osteoporotic population. The outcome measures being used for this are the bone turnover markers CTX-I (C-terminal telopeptide of type I collagen) a marker that reflects the breakdown of bone and PINP (N-terminal propeptide of type I collagen) a marker that reflects the formation of new bone. The primary end point will be the difference in these bone turnover markers after 48 weeks between both treatment arms.

4.2 Secondary endpoints

Secondary end points are changes in bone mineral density (BMD) at the femoral neck and spine at week 48, the number of patients from both groups maintaining CTX-I and PINP levels within reference range values at week 12, 24 and 48. Reference ranges used will be adjusted according to menopausal status and sex. Percentage changes in BMD and the percentage of patients with a BMD loss higher than the least significant change (LSC), which represents the smallest difference between successive measurements of BMD that can be considered a real change, will be calculated.

4.3 Safety data

Analysis of the safety data set will be performed. This will include the occurrence on incidence and severity of adverse events and serious adverse events. These will be categorized according to the involved organ systems. The number of the events will be reported and compared between both treatment groups. Changes in routine clinical laboratory tests (calcium, vitamin D, creatinine, urine and GFR) will also be analyses

4.3 Exploratory outcomes measures

Exploratory end points are the development of new erosive joints (using the Verbruggen and Veys anatomical phase scoring system) (2) and hand pain scores, measured using a NRS pain scale at week 48.

5. Statistical analysis

All statistical analyses will be performed using R and RStudio (version 4.1.1).

All continuous variable will summarized using mean and standard deviation (SD). Frequency count and percentages will be used to summarise categorical variables.

5.1 Summary of baseline data

A brief summary of descriptive statistics will be provided including demographic features and disease specific characteristics. Demographic baseline data will be compared between both treatment groups.

5.2 Primary outcome analysis

The primary outcome analysis will be performed in an intention to treat approach, where drop-outs were considered as non-responders. Changes in bone turnover marker levels will be analysed with a linear mixed model. Data from all available time points will be used. Normal distribution will be checked and data transformations will be performed if necessary if assumptions of normality aren't reached. P-values and estimated marginal means will be calculated at different time points.

All analyses will be performed with a two-sided p-value. A p-value below 0.05 ($p<0.05$) will be considered statistically significant.

5.3 Secondary outcome analysis

Bone density measures will be analysed in an intention to treat approach, using a linear mixed model. Data from all available time points will be used. Normal distribution will be checked and data transformations will be performed if necessary if assumptions of normality are not reached. P-values and estimated marginal means will be calculated at different time points.
In addition, percentage changes in BMD and the percentage of patients with a BMD loss higher than the least significant change (LSC), which represents the smallest difference between successive measurements of BMD that can be considered a real change, will calculated. Here no intention to treat approach will be used.
The number of patients exceeding reference ranges will be calculated with an intention to treat approach, where drop-outs will be considered as non-responders. A Fisher's exact test was used to assess differences in patient numbers exceeding reference ranges between both treatment groups.

All statistical tests were two-tailed and a p-value below 0.05 (α) was considered statistically significant.

5.4 Exploratory outcome measure analysis

Hand pain scores will be analysed using an intention to treat approach, using a linear mixed model. Data from all available time points will be used. Normal distribution will be checked and data transformations will be performed if necessary if assumptions of normality are not reached. P-values and estimated marginal means will be calculated at different time points. Changes in new erosive joint count on radiographs, scored using the Verbruggen and Veys anatomical phase scoring system (2) and hand pain scores, measured using a NRS pain scale at week 48. The number and percentage of joints in each radiographical phase (N, S, J, E and R phase) will be reported. The total number and percentage of pre-erosive joints (N,S and J phase) progressing to an erosive phase during the trial will also be reported.

6. Timeline

The SAP will be finalized prior to the database lock. The last visit of the last patient was foreseen in March 2022. Data lock will be done after June 2022. Statistical analyses will be performed from June 2022 till approx. end of January 2023. Report to be expected Beginning of March 2023.

7. References

1. Wittoek R VG, Vanhaverbeke T, Colman R, Elewaut D. . RANKL-blockade for erosive hand osteoarthritis: A randomized, placebo-controlled phase 2a trial. . Nature Medicine (accepted for publication). 2024.
2. Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. Arthritis Rheum. 1996;39(2):308-20.