A randomized, double-blind, placebo-controlled, dose escalation study to evaluate the safety and tolerability of subcutaneous immunotherapy with DM-101 in adults with birch pollen allergy

Study code: DM-101-C-001

Phase I study

STATISTICAL ANALYSIS PLAN

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1 Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIT	Allergen Immunotherapy
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
ECG	Electrocardiogram
FSH	Follicle stimulating hormone
FIH	First In Human
IMP	Investigational Medicinal Product
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPT	Skin Prick Test
SRC	Safety Review Committee
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
WAO	World Allergy Organization

2 General remark

After inclusion of 11 subjects (6 subjects in cohort 1 and 5 subjects in cohort 2), the further recruitment of study subjects was halted on 17th March 2020 due to the Covid-19 epidemic. Re-start of dosing was not recommended by the Safety Review Committee because of the impending start of the birch pollen season of 2020 and occurrence of significant AEs in cohort 2. The data of the 11 subjects so far included in cohorts 1 and 2 were analyzed according to the statistical analysis plan (SAP) version 13.5.2020 and summarized in an interim report dated 18th September 2020. Based on the safety findings in cohort 2, the study design was amended after the temporary halt to include only 2 additional cohorts (cohorts 3 and 4) where DM-101 was to be administered following a slowly escalating biweekly repeated dose regimen, with doses starting from 30 ng, up to a maximum of 300 ng. This SAP describes the analysis of all 4 cohorts, considering the amended study design (protocol version 3.1).

3 Study objective(s)

The primary objective of the study is to evaluate the safety and tolerability of subcutaneous (s.c.) administration of DM-101 in adult subjects with birch pollen allergy. A secondary objective is to determine the proportion of study subjects who reach the pre-defined maximum admissible s.c. DM-101 dose in each dosing group.

An exploratory objective of the study is to evaluate the possible effects of repeated s.c. DM-101 dosing on immunological biomarkers in study subjects with birch pollen allergy.

4 Design and type of the study

The study is a randomized, double-blinded, placebo-controlled, dose escalation study to evaluate the safety and tolerability of subcutaneous immunotherapy with DM-101 in adults with birch pollen allergy.

5 Sample size considerations

After the protocol amendment, a total of 27 subjects were planned to be randomised into the study. For cohort 1, 6 subjects were randomized in a ratio of 2:1 to receive single doses of DM-101 or placebo. For cohort 2, 5 subjects were randomized before the temporary halt of the study, 4 to receive repeated doses of DM-101 and one to placebo. For cohorts 3 and 4, the following allocation was planned:

Cohorts 3 and 4: 8 subjects per cohort randomized in a ratio of 3:1 to receive repeated doses of DM-101 or placebo.

6 Statistical hypotheses

There are no formal statistical hypotheses set for the study.

7 Analysis sets

A subject classification document including a list of protocol deviations with a clinical classification of the deviations and the definition of the analysis datasets will be prepared and

approved after database lock before opening of the randomization code. For cohorts 1 and 2, subject classification was already done prior to opening of the randomization code of these cohorts for the interim analysis and report (documented in Desentum DM-101-C001 Subject Classification Final 18May2020.doc). The subject classification of cohorts 3 and 4 will be done after the database lock of the full database and prior to opening of the randomization code of these two remaining cohorts.

Three main analysis data sets were planned to be constructed. The intent-to-treat (ITT) data set was to include all subjects having received study medication and providing at least a minimum amount of relevant measurements. The safety data set was to consist of subjects having received at least one dose of study medication. The per protocol (PP) data set was to exclude all subjects from the ITT data set who meet any of the predefined criteria in the subject classification document.

8 General statistical considerations

The data will primarily be analysed using summary statistics. Summary statistics will include at least the number of subjects, mean, standard deviation, median, minimum and maximum values for continuous variables, and frequencies and percentages for categorical variables. All data collected will be listed by subject, cohort, and treatment. In case inferential statistical analyses are conducted, a 2-sided p-value of less than 0.05 is considered statistically significant.

9 Demographic and other baseline characteristics

The demographic variables (age, gender, race, ethnicity, height, weight and body mass index) and baseline characteristics (including results of skin prick testing and Bet1v IgE as well as other than Birch common allergen IgE screening levels and pregnancy test results of females of child-bearing potential) and medical history of the subjects will be presented using descriptive summary statistics or frequency tables by cohort and treatment.

10 Prior and concomitant medication/treatment

Prior and concomitant medications will be classified according to ATC and reported by ATC1, ATC4, cohort and treatment group using descriptive tables and listings. Any medication started and ended prior to start of study treatment is considered prior medication and medication ongoing or ended after start of study treatment is considered as concomitant medication. Separate summaries for medication used to treat an adverse event will be given.

11 Extent of exposure and compliance

Used doses with a cumulative received dose will be summarized descriptively for each cohort and each subject. Also, the numbers of subjects receiving each planned dose and the number of changes from planned doses will be summarized with percentages.

12 Analysis of efficacy

Not applicable.

13 Analysis of of safety variables

The primary endpoint of the study is the number of all treatment-emergent adverse events (TEAEs) in subjects receiving treatment with DM-101, compared to placebo. TEAEs will be MedDRA coded and tabulated by System Organ Class and Preferred Term. Occurrence of single Preferred Terms will be presented by cohort and treatment. In addition, TEAEs will be reported by causality and severity. Both subject and event counts will be summarized. Adverse events occurring prior to first administration of study drug will be listed.

The number and severity of systemic allergic reactions in subjects receiving treatment with DM-101, compared to placebo, will be presented in a similar manner as the TEAEs.

Systemic allergic reactions (SAR) are described with case narratives and will be graded per WAO classification and summarized by cohort and treatment. In addition, an overall summary of SARs by grade, causality, severity, seriousness, and concomitant/additional treatment given (yes/no) will be created. SARs by onset (dosing day and immediate vs delayed (>30 min from dosing)) will be summarized as well. Local injection site reactions (pain, tenderness, erythema/redness, induration/swelling) will be graded on a five-point (0 to 4) scale. These will be summarized by cohort and treatment and presented separately for each cohort (including by injection). Also, a summary by onset (immediate vs. delayed (>30 min from dosing)) will be given and the size of the measured skin reaction for all cohorts (using the collected precision) will be summarized by subject over time and compared to the dose of each injection.

Other safety variables include results from physical examination, vital signs, clinical laboratory values and spirometry. The results will be presented using descriptive statistics and visualizations by cohort, time point and treatment. For the laboratory assessments, all out-of-range values and their clinical significance (CS) (categories: low[CS], low[NCS], normal, high [NCS], high [CS]) will be summarized with shift tables for change from baseline. If feasible, also these parameters and changes from pre-dose to post-dose can be compared to the cumulative dose. Tryptase values will be listed by subject and time point (measured only for subjects with suspected grade 3 or higher systemic allergic reaction or anaphylactic shock).

14 Analysis of other variables

The proportion of subjects reaching the pre-defined, cumulative dose in each DM-101 treatment group is one of the secondary endpoints. It will be summarised using descriptive statistics.

15 Analysis of exploratory variables / Immunological biomarkers

Descriptive statistics and visualizations will be provided for Allergen-specific IgE levels (for components Bet v 1, Bet v 2, Bet v 4 and Bet v 6), and immunological biomarkers (such as IgG sub-classes and IgA). Bet v 1 and immunological biomarker results may be presented also in relation to the cumulative received dose for cohorts 3 and 4. Exploratory statistical analysis may be used to illustrate the association of dose received and biomarker levels, if feasible.

16 Completion and premature discontinuation

Completions and premature discontinuations will be tabulated and listed. The reasons for premature discontinuations will be presented.

17 Deviations from the analyses planned in the study protocol

No deviations of the statistical analysis plan are considered from the current protocol version (3.1).

18 Execution of statistical analyses

Statistical analyses will be performed by 4Pharma Ltd. according to the company's SOPs.

19 Hardware and software

Statistical analysis and preparation of tables and subject data listings will be performed with SAS® version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

20 References

Clinical Study Protocol, Final Protocol version 3.1(**25 January 2021**).

21 Appendices

21.1 Table and figure plan

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