CLINICAL STUDY PROTOCOL

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**

EudraCT No: **2019-001936-67**

Phase: **I**

Sponsor: **Desentum Oy**

Principal Investigator:

Protocol Version: **3.1 Final**

Protocol Date: **25 Jan 2021**

SIGNATURES

Principal Investigator: _____ Date: _____/_____/_____

Clinical Research Services Turku - CRST Oy

Biostatistician: _____ Date: _____/_____/_____

Oy 4Pharma Ltd.

Representative
of the Sponsor: _____ Date: _____/_____/_____

Desentum Oy

Medical Monitor
of the Sponsor: _____ Date: _____/_____/_____

CONTACT INFORMATION

Principal Investigator

Sponsor's Medical Monitor

Sponsor's contact person

Data Management & Biostatistics

Pharmacovigilance

SAE reporting:

Safety Laboratory

Allergen specific IgE screening laboratory

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APPENDICES

SYNOPSIS

Name of the Sponsor/Company: Desentum Oy
Name of the finished product: DM-101 Drug Product
Name of the active ingredient: DM-101
Study code: DM-101-C-001, EudraCT No: 2019-001936-67
Study title: 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
Investigators and study centres: Principal Investigator, Clinical Research Services Turku - CRST Oy, Finland
Development phase: I
Objectives: **Primary Objective:** To evaluate the safety and tolerability of s.c. administration of DM-101 in adult subjects with birch pollen allergy. **Secondary Objective:** To determine the proportion of adult subjects who reach the pre-defined maximum admissible s.c. DM-101 dose in each dosing group. **Exploratory Objective:** To evaluate the possible effects of repeated s.c. DM-101 dosing on immunological biomarkers in adult subjects with birch pollen allergy.
Methodology: The study is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and tolerability of DM-101 s.c. administration in subjects with birch pollen allergic rhino-conjunctivitis. The study is planned to be conducted outside of the birch pollen season in Finland. The study will include up to 4 cohorts of participants. In each cohort, subjects are randomly allocated to receive s.c. doses of DM-101 or placebo. Cohort 1 includes a single dose administration. Cohorts 2 to 4 include escalating, repeat dose administration. The study starts with cohort 1 and sequentially proceeds to cohorts 2, 3 and 4. Dose escalation will be initiated only upon satisfactory review of all available safety data from previous dose levels and favourable recommendation from the study's Safety Review Committee.

Cohort 1 was completed and dosing in cohort 2 was initiated in the first quarter of 2020. The study was temporarily halted on the 17th of March, 2020, during the conduct of cohort 2 due to the COVID-19 pandemic. An interim analysis of the obtained results from cohorts 1 and 2 was performed, and based on the findings, a substantial amendment to the study protocol was prepared (protocol version 2.0). The amended protocol version 2.0 includes adjustment of the study design and dosing regimens for cohorts 3 and 4.

The study includes a screening, a treatment and a follow-up period.

For cohort 1 (single dose) the study consists of 3 visits: Visit 1 screening; Visit 2 baseline and dosing; Visit 3 follow-up 28 days after the dosing.

For cohort 2 the study was to consist of 7 visits: Visit 1 screening; Visit 2 (Day 1 and Day 2) baseline and dosing on Day 1 (6 ascending doses) and on Day 2 (3 ascending doses); bi-weekly Visits 3-6 with single dosing (dose equaling to the highest safe and well-tolerated single dose of Day 2); Visit 7: follow-up 28 days after the last dosing.

Cohort 2 was halted after partial completion of Visit 2 of 5 of the planned 8 participants. Cohort 2 procedures will not be re-started according to protocol version 2.0.

For cohort 3 the study consists of 7 visits: Visit 1 screening; Visit 2 baseline and dosing of a single injection; bi-weekly Visits 3-6 with dosing of single injections; Visit 7: follow-up 28 days after the last dosing.

For cohort 4 the study consists of 7 visits: Visit 1 screening; Visit 2 baseline and dosing of a single injection; bi-weekly Visits 3-4 with dosing of single injections; Visits 5-6 dosing of 2 and 3 injections in each, respectively; Visit 7: follow-up 28 days after the last dosing.

Dosing and follow-up on Visits 2-6 is planned to take place within the premises of Turku University Hospital, in its Emergency Care Unit. A qualified physician will be present at the site throughout the confinement periods of the study subjects.

In every cohort a sentinel group of 2 subjects, 1 receiving DM-101 and 1 receiving placebo, is planned to be dosed first in a double-blind fashion. Treatment of the remaining subjects in the cohort can be initiated no sooner than 22 hours after the sentinel subjects have completed their dosing without safety findings. The rest of the subjects in the cohort are also planned to receive their doses in a staggered fashion.

Dose levels and dosing schedules are provided in Table 2 and 8 for all cohorts and a schematic of the study design is presented in Figure 1.

Number of Subjects:

Approximately 27 subjects are planned to be randomised into the study.

Cohort 1: 6 subjects were randomized in a ratio of 2:1 to receive single doses of DM-101 or placebo.

Cohort 2: 8 subjects were to be randomized in a ratio of 3:1 to receive repeated doses of DM-101 or placebo, but only 5 of the planned 8 subjects were included before the study was temporarily halted. Due to the protocol amendment (version 2.0), no more subjects are planned to be randomized into cohort 2.

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

Main eligibility criteria:

Inclusion Criteria

1. Males or females, aged 18 to 65 years inclusive.
2. Good general health, as determined by the Investigator, based on medical evaluation, including medical history, physical examination, laboratory tests and electrocardiogram (ECG).
3. A documented clinical history of birch pollen-induced allergic rhinitis or rhino-conjunctivitis with symptoms that interfere with daily activities or sleep and remain bothersome despite the use of relevant symptomatic medication, and have been present over, at least, 2 allergy seasons.
4. Bet v 1 specific serum IgE ≥ 0.7 kU/L (class 2), measured by ImmunoCAP®.
5. Positive SPT to birch pollen allergen, with a wheal diameter ≥ 5 mm (average of longest and orthogonal) greater than that produced by the negative control.
6. Body weight ≥50 kg and body mass index (BMI) within the range 18–35 kg/m^2.
7. Females are eligible to participate only if they are of:
- non-childbearing potential, defined as pre-menopausal females with documented tubal ligation or hysterectomy, or postmenopausal, defined as 12 months of spontaneous amenorrhea (in questionable cases a blood sample with levels of follicle stimulating hormone (FSH) > 40 MIU/ml and estradiol < 40 pg/ml (<147 pmol/L) is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods in Section 4.3.1.1. if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks should elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume the use of HRT during the study without the need to use a contraceptive method.
- child-bearing potential and have a negative serum pregnancy test result at Screening and a negative serum pregnancy test result within 10 days prior to the first dosing visit, a negative urine pregnancy test before each subsequent dosing and agree:
- to use one of the contraception methods listed in Section 4.3.1.1. starting at least 2 weeks prior to the start of dosing to sufficiently minimize the risk of pregnancy during the treatment period of the study. Female subjects must agree to use contraception until 30 days after the last treatment administration.
- or abstains from sexual intercourse or has only same-sex partner(s), when this is her preferred and usual lifestyle.

8. Males who are sexually active with a female partner of childbearing potential must agree to use one of the contraception methods listed in Section 4.3.1.2.
9. Willing and able to provide written informed consent.
10. Willing and able to comply with the study requirements.

Exclusion Criteria

1. History or findings on physical examination of any significant disease or disorder (e.g. cardiovascular, pulmonary, gastrointestinal, hepatic, renal, neurological, immunological, musculoskeletal, endocrine, metabolic, major psychiatric, major physical impairment, cancer) which, in the opinion of the Investigator, may put the subject at risk because of participation in the study, influence the results of the study or the subject's ability to participate in the study.
2. Current diagnosis of asthma (other than seasonal during the birch pollen allergy season), requiring Global Initiative for Asthma (GINA) Step 2 or higher treatment, or

	asthma partially controlled or uncontrolled according to GINA classification in the 6 months before Screening.
3.	History of asthma deterioration that resulted in emergency treatment or hospitalisation in the 12 months before screening, or a life-threatening asthma attack (e.g. one requiring intubation and mechanical ventilation) at any time in the past.
4.	Forced Expiratory Volume in one second (FEV_1) < 70% of predicted, regardless of asthma status at screening or baseline assessment at the first dosing visit.
5.	History of severe drug allergy, severe angioedema or systemic allergic reaction of Grade 3 or greater, according to the World Allergy Organization (WAO) scale, due to any cause.
6.	Use of systemic glucocorticoid medication within 30 days prior to Screening.
7.	Use of anti-IgE medication within 3 months prior to Screening.
8.	Use of mast cell stabilisers, anti-leukotriene agents or anti-histaminics less than 1 week prior to dosing initiation.
9.	A course of short-duration allergen-specific immunotherapy or more than 3 months' treatment with long-duration allergen immunotherapy, within five years prior to Screening.
10.	History of intolerance to the study drug, rescue medications (i.e. adrenaline, antihistaminics, glucocorticoids), or their excipients.
11.	Regular use of angiotensin-converting enzyme inhibitors, beta-adrenergic blockers or monoamine oxidase inhibitors.
12.	Ongoing treatment with substances interfering with the immune system.
13.	Treatment with an investigational drug within 30 days prior to Screening or concurrent participation in another clinical trial.
14.	Contraindication for the administration of adrenaline (e.g. subjects with acute or chronic symptomatic coronary heart disease or severe hypertension).
15.	Significant history of alcohol or drug abuse in the past 5 years, or a positive Screening or pre-dose drug/alcohol test result. A positive screening result for benzodiazepines or opioids may be accepted at the discretion of the investigator, if the finding can be satisfactorily explained by the subject's medical history and concomitant medication information.
16.	Females who are pregnant, lactating or planning to become pregnant, or plan to donate oocytes for *in vitro* fertilisation during the study treatment period or within 30 days following the treatment period. Subjects unwilling to employ appropriate contraceptive measures to ensure that pregnancy will not occur either during or for 30 days following the completion of the treatment period.

Investigational drug, dose and mode of administration:

DM-101 Drug Product is a sterile solution for s.c. injection
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Mode of administration: s.c. injection

Reference drug(s)/placebo, dose and mode of administration:
Placebo: Diluent for DM-101

Route of administration: s.c. injection

Duration of treatment: **Cohort 1**: 1 day, single dose administration. **Cohorts 2, 3 and 4:** 8 weeks, including 5 bi-weekly administrations
Assessments: Safety: Treatment Emergent Adverse Events (AE), including systemic allergic reactions and local injection site reactions Other safety variables: results of physical examination, vital signs, clinical laboratory values and spirometry Immunological Biomarkers Bet v 1 specific serum levels of IgE Other explorative biomarkers

ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIT	Allergen Immunotherapy
CA	Competent Authority
CRF	Case Report Form
CRO	Contract Research Organisation
CRST	Clinical Research Services Turku
DM	Data Management
DMP	Data Management Plan
EAACI	European Academy of Allergy and Clinical Immunology
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
FSH	Follicle stimulating hormone
FIH	First In Human
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ICMJE	International Council of Medical Journal Editors
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ISF	Investigator study file
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
ISF	Investigator Site File
NOAEL	No-Observed Adverse Effect Level
NtF	Note to File
PI	Principal Investigator
PV	Pharmacovigilance
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SPT	Skin Prick Test
SRC	Safety Review Committee
S.C.	Subcutaneous
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse drug reaction
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
WAO	World Allergy Organization

WOCBP Women of Childbearing Potential

Abbreviations used for major birch pollen allergen Bet v 1 and its derivatives

Bet v 1	Naturally occurring major birch pollen allergen, native wild-type Bet v 1
Bet v 1 d	Naturally occurring hypoallergenic isoform of major birch pollen allergen Bet v1
rBet v 1	Recombinant Bet v 1
rBet v 1 d	Recombinant hypoallergenic isoform Bet v 1 d
rBet v 1 dm	Investigational Medicinal Product DM-101

1. INTRODUCTION

1.1. Background

Allergic diseases, including allergic rhinoconjunctivitis and allergic asthma, are common immunoglobulin E (IgE) hypersensitivity (type I) mediated immune disorders that affect a significant proportion of the population of all ages. Their prevalence is increasing world-wide and they add considerably to the cost burden of health care (Bauchau, 2004; Calderón, 2012). Pollens are one of the most frequent triggers of allergic symptoms. It is estimated that about 40 % of allergic subjects are sensitised to pollen allergens and suffer from seasonal allergy symptoms during the pollination season (D'Amato, 2007). Among those individuals, approximately one quarter are allergic to birch (*Betula verrucosa*) pollen. Birch and a related group of deciduous trees, which includes alder, beech, hazel and oak, are the most common cause of tree pollen-triggered respiratory allergies in Northern and Central Europe and North America. It is estimated that around 15 million Europeans have birch pollen allergies of which about 10 % are believed to have symptoms that are not well controlled by conventional, symptom-relieving medications. The main allergen in birch pollen is "Bet v 1", and more than 95 % of tree pollen allergic patients possess IgE antibodies against it (Jarolim, 1989; Sekerková, 2011). Due to cross-reactivity, approximately 70 % of subjects allergic to fruits and vegetables are also sensitised to Bet v 1.

Allergic pathogenesis is caused by aberrant generation of allergen-specific Th2 cells with an effector phenotype. The Th2 cells, through the cytokines they secrete (i.e. IL-4, IL-5, IL-9, IL-13), drive the two critical elements responsible for the manifestation of allergic symptoms: a) increased synthesis of allergen-specific IgE, which mediates the type I hypersensitivity reactions, and b) differentiation, survival and chemotaxis of pro-inflammatory cells, namely mast cells, basophils and eosinophils, that orchestrate the development of chronic inflammation (Broide, 2001; Kay , 2006). Therapeutic modulation of these immune cascades that underlie the disease pathology holds the key for successful "curative" treatment of allergic disorders. Currently, the management of pollen-induced allergies relies primarily on allergen avoidance and use of pharmacotherapy which can offer symptom control and suppression of local inflammation. Topical glucocorticoids and anti-histaminics are the most common prescription medications (Meltzer, 2013). This approach is clearly beneficial, but it is not curative and requires continuous use of medication to maintain the clinical effect. The only therapeutic modality that prevents allergic symptoms through alteration of the dysfunctional immune mechanisms is specific Allergen Immunotherapy (AIT). Specific AIT can achieve effective symptom control, enhanced tolerance to allergen exposure, modulation of disease progress and potentially disease remission (Eifan, 2011; Calderón, 2012; Roberts, 2018). Extended meta-analyses of the results of all valid relevant clinical trials have confirmed the efficacy of AIT for pollen-driven allergic rhinoconjunctivitis (may be up to 60 - 90 % in fully compliant patients), as well as its cost-effectiveness compared to standard pharmacotherapy (Calderón, 2012; Nurmatov, 2017; Roberts, 2018). How AIT achieves its benefit is not entirely clear, but there is evidence that restriction of allergen-specific Th2 and IgE activity takes place. This may be due to a number of treatment-induced changes, such as increased production of protective allergen-specific immunoglobulin G4 (IgG4) and immunoglobulin A (IgA) antibodies, decreased release of allergic mediators, up-regulation of counter-balancing regulatory T cells and inhibition of tissue infiltration by allergy effector cells (Akdis, 2014; Penagos, 2018).

AIT involves repeated administration of the relevant allergen (via subcutaneous (s.c.) injection or orally/sublingually) for long periods of time, usually 3-5 years. Typically, AIT starts with a build-up phase, during which the allergen doses are progressively escalated, followed by a maintenance phase where a high, well tolerated, allergen dose is given regularly for a prolonged period. The better established and widely used forms of AIT include administration of natural allergen extracts. Despite its promising efficacy, AIT with natural allergens is associated with several limitations, including poor adherence due to the long duration of treatment, variable treatment responses because of the often-questionable quality of allergen extracts and concerns for serious side effects, such as severe allergic reactions (Roberts, 2018). The magnitude and duration of the AIT benefit seems to be related to the total (cumulative) dose of the administered allergen. When natural allergens are used, the maximum cumulative dose that can be achieved is restricted and requires a long treatment period to be delivered in a safe manner (Calderón, 2011; Penagos, 2018; Worm, 2018). To reduce the duration of s.c. AIT, various rush and ultra-rush dose escalation protocols have been successfully developed and applied in clinical practice (Cox, 2006; Calabria, 2013). These protocols include fast increase of the allergen doses, over a very short build-up phase, in order to induce quick desensitization and to facilitate early initiation of the maintenance phase. Maintenance treatment for several years is, however, still required to achieve a high cumulative allergen dose and long-lasting benefit (Calderón, 2011).

To address the existing challenges with current forms of AIT and to offer an alternative, highly safe, short-course approach with allergenic products manufactured through a standardized, reliable process, Desentum Oy has developed a novel type of hypoallergen with low IgE reactivity potential. This has been achieved with the use of recombinant DNA technology and substitution of the key amino acids in the allergenic molecule that determine its binding to IgE on the surface of allergy effector cells. Because of these alterations, the Desentum product has reduced capacity to trigger IgE-mediated hypersensitivity reactions. Therefore, if the product is used in AIT regimens, it may allow quick dose escalation to high dose levels, without induction of allergic Adverse Events (AE).

1.2. Rationale

DM-101 is Desentum's modified, recombinant, hypoallergenic variant of Bet v 1, the major allergen responsible for the allergenicity of birch pollen. DM-101 is very similar to the native antigen, wild-type Bet v 1, with the exception of amino acid substitutions (DM-101 Investigator's Brochure (IB)). The preservation of the great majority of molecular sequence and the three-dimensional structure allows DM-101 to retain the capacity to bind effectively to Bet v 1-specific immunoglobulin G (IgG) antibodies, while the amino acid substitutions, result in reduced IgE binding capacity. Moreover, the introduction of these substitutions disrupts the ability for IgE monomer-monomer interaction and formation of dimers. This further reduces the allergenic potential, as effective IgE receptor cross-linking on the surface of mast cells and basophils and subsequent release of allergic mediators requires the presence of IgE dimers.

The immunogenic profile of DM-101 has been assessed in a series of pre-clinical studies. *In vitro* histamine release experiments, using serum from birch pollen allergic patients, overall indicate that the release of histamine following stimulation of basophils with DM-101 is reduced compared to the wild-type rBet v 1 allergen (DM-101 IB). Specifically, in

the initially (2010-2014) conducted histamine release assays, the EC_{50} values for the wild-type rBet v 1 have been between 0.08 nM - 0.95 nM, while for DM-101 they have been between 1.66 nM - 59.0 nM (DM-101 IB). This corresponds to an EC_{50} ratio of DM-101 to wild-type rBet v 1 ranging from 7.1 to 117.8 (Table 1).

Table 1 Results of histamine release assays with recombinant wild-type Bet v 1 (rBet v 1 wt), DM-101 and the recombinant hypoallergenic isoform Bet v 1 d (rBet v 1 d)

Study timepoint	Serum sample	rBet v 1 wt EC50 [nM]	DM-101 EC50 [nM]	rBet v 1 d EC50 [nM]	DM-101 / rBet v 1 wt EC50	rBet v 1 d / rBet v 1 wt EC50
Jul 2010	Subject 1	0,95	6,94		7,3	
Jul 2010	Serum pool	0,48	3,37		7,1	
Feb2014	Subject 1	0,23	1,66	4,97	7,2	21,6
Jul 2014	Subject 1	0,18	2,40	5,16	13,3	28,6
Jul 2014	Subject 2	0,76	15,00	14,70	19,7	19,3
Jul 2014	Subject 3	0,53	8,30	7,28	15,7	13,7
Jul 2014	Subject 4	0,08	3,40	0,62	40,5	7,4
July 2014	Subject 5	0,37	4,40	3,40	11,9	9,2
July 2014	Subject 6	0,17	3,70	3,75	21,8	22,0
Sep 2014	Subject 1	0,22	14,00	5,46	65,2	25,4
Sep 2014	Subject 2	0,92	59,00	12,00	64,1	13,0
Sep 2014	Subject 3	0,45	53,00	7,32	117,8	16,3
Sep 2014	Subject 4	0,12	6,10	1,72	49,2	13,9

EC50: Half maximal effective concentration

Histamine release experiments performed some years later (in 2017), using the same serum samples, but freshly acquired basophils from different donors, showed a smaller overall difference in the allergenic potential of DM-101 compared to wild-type rBet v 1. In these later experiments the EC_{50} values for the wild-type rBet v 1 have been between 0.036 nM - 0.261 nM, while for DM-101 they have been between 0.041 nM – 0.370 nM (DM-101 IB). It is likely that the unstandardized nature of the assay and the use of basophils from different donors over the years may account for the observed variations in test sensitivity. Please see the DM-101 IB for more information.

In vivo studies support that the ability of DM-101 to activate generation of Bet v 1-specific blocking IgG antibodies, a key mechanism of the AIT-mediated development of allergen tolerance (Akdis, 2014; Penagos, 2018), remains intact (DM-101 IB). Studies in a birch pollen sensitized mouse model have demonstrated that repeated s.c. administration of DM-101 leads to induction of high Bet v 1-specific IgG levels and reduction of specific IgE levels, comparable to that achieved following s.c. administration of the wild-type allergen (DM-101 IB). This is a significant difference compared to some other forms of birch

hypoallergens under development that do not appear to be associated with significant induction of specific IgG upon treatment (Lund, 2007).

The non-clinical safety of DM-101 has been evaluated in birch pollen sensitized mice. No differences in safety parameters have been observed following a single, high dose (10 µg) intravenous administration of DM-101 and analogous, control administration of wild-type rBet v 1 (DM-101 IB). Furthermore, no significant effects have been observed in the standard 10 weeks toxicity studies in rabbits, at s.c. DM-101 doses up to 500 µg / animal (approximately 125 µg /kg) administered every 2 weeks. Based on the completed non-clinical program, the No-Observed Adverse Effect Level (NOAEL) is set at 500 µg, the highest dose tested non-clinically for toxicity (DM-101 IB). This provides an approximately 15-fold safety margin to the highest DM-101 dose level (500 µg, 8.3 µg/kg) originally planned to be administered in this First In Human (FIH) trial, had clinical safety observations allowed it (see protocol version 1.1). It also provides an approximately 16,000-fold safety margin to the starting dose (30 ng) of this FIH study.

1.2.1. Study Rationale

Given the attractive characteristics of DM-101, Desentum aims to pursue its pharmacological development as a novel form of AIT for subjects with birch pollen-driven allergic disease and will now initiate a FIH evaluation. The proposed evaluation of the safety and tolerability of DM-101 is in accordance with the European Medicines Agency (EMA) guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases (CHMP/EWP/18504/06). Successful completion of this study will provide the necessary supporting evidence to proceed to further evaluation of the safety and efficacy of a short course of DM-101 AIT in larger clinical trials.

Classical phase I studies in healthy individuals are not appropriate for AIT products, since they do not provide helpful safety information, as non-allergic individuals do not react like allergic subjects and therefore they do not carry the risk of the targeted population. For this reason, the DM-101 FIH study will be conducted in subjects with a history of moderate to severe allergic rhinoconjunctivitis during the birch pollen season and confirmed sensitization to birch pollen allergen.

Usually, FIH trials start with evaluation of single, ascending doses of the Investigational Medicinal Product (IMP), followed by multiple ascending dose evaluation until a safe and well tolerated dose range and dosing regimen are established. The targeted maximum dose is usually pre-defined in the study protocol, based on preceding non-clinical evidence. However, in the case of AIT products, assessment of the safety and tolerability of single doses does not necessarily provide appropriate information, as most AIT schedules include continuous dose escalation until a maximum tolerated or protocol-defined target (maintenance) dose is reached. The continuous dose escalation induces immunological changes, associated with allergen desensitization, that reduce the risk of allergic reactivity following subsequent dose administration, compared to the risk carried by single administration of the allergenic product, without prior exposure to it. To permit, therefore, appropriate evaluation of the safety and tolerability of DM-101, a repeat dose escalation regimen, previously employed in AIT protocols for pollen-driven respiratory allergies (Calabria 2013; Winslow, 2016), was included in the FIH study plan (protocol version 1.1). The FIH study was initiated in February 2020, but temporarily halted because of the Covid-19 pandemic on 17th March 2020, during the conduct of cohort 2.

During the conduct of the rapid, repeat dose escalation phase regimen included in cohort 2, safety findings were observed in all subjects dosed with DM-101. The findings did not meet the study's stopping criteria but indicated that the maximum tolerated dose of DM-101 is lower than initially anticipated. For this reason, the originally planned rapid dose escalation regimen has been amended (study protocol version 2.0). In the amended study protocol, a much slower and limited dose escalation is proposed, based on the findings from cohorts 1 and 2 of the study. This amended dosing regimen is expected to be well tolerated, but still capable of providing relevant information for further product development.

1.2.2. Original Dose Selection Rationale (Protocol version 1.1)

The doses of DM-101 to be tested in this FIH study (Table 2) have been selected based on the allergen doses commonly employed in various s.c. birch AIT protocols and the non-clinical evidence derived from Desentum's experiments, showing that the allergenic potency of DM-101 is lower than that of the native Bet v 1 allergen.

Standard s.c. AIT with natural birch pollen extracts has being extensively used in clinical practice and has been found effective in reducing symptoms and medication needs during the pollen season, in subjects with moderate to severe birch pollen allergy (Moingeon, 2016). The clinical benefit appears to be related to humoral immune changes, such as inhibition of IgE binding and IgE-facilitated allergen presentation, associated with decreased serum concentrations of Bet v 1-specific IgE and increased levels of Bet v 1-specific IgG4 (Moingeon, 2016). Most regimens of s.c. AIT with standardized, commercially available birch pollen extracts (i.e. Betula Verrucosa Alutard SQ, ALK-Abello) start with doses of 10-20 SQ-U which equals to **1.23-2.46 ng** of allergen and progressively escalate to a maintenance dose of 100,000 SQ-U which equals to **12,300 ng** (Arvidsson, 2002; Bodtger, 2002; Larenas-Linnemann, 2008; Wurtzen, 2008).

A recombinant form of the native, wild-type Bet v 1 (rBet v 1) has also been developed and used for AIT. Results from controlled clinical trials demonstrate that native rBet v 1 AIT has an excellent safety profile and equivalent efficacy to s.c. AIT with natural birch pollen extracts (Pauli, 2008). Regimens of s.c. AIT with the native rBet v 1 usually start with **50 ng** and following escalation reach a maximum dose of **15,000 ng** per injection (Pauli, 2008).

To improve the safety of birch pollen AIT, three types of hypoallergenic derivatives of the native rBet v 1, a mix of two fragments of rBet v 1, a trimer of rBet v 1 and a folding variant of rBet v 1 (rBet v 1-FV) obtained by alkaline denaturation, have been developed and assessed in the clinic (Moingeon, 2016). The s.c. AIT regimens using the mix of two rBet v 1 fragments or the rBet v 1 trimer employ much higher starting doses (**1,000 ng**) and escalate progressively to a maintenance dose of **80,000 ng** per injection (Niederberger, 2004; Reisinger, 2005; Purohit, 2008). Regimens with analogous doses of rBet v 1-FV have also been tested, as well as a regimen with repeat administration of single s.c. doses of 20,000 ng, 80,000 ng, 160,000 ng or **320,000 ng** of rBet v 1-FV once weekly for 10 weeks (Meyer, 2013; Klimek, 2015). All three forms of hypoallergenic birch s.c. AIT have been found to be safe, despite the high doses of the rBet v 1 derivatives administered.

The current study will initially evaluate the safety and tolerability of single administration of **30 ng** of DM-101 in cohort 1 (Table 2). This dose is below the starting doses employed in s.c. AIT protocols with wild-type rBet v 1 or other hypoallergenic rBet v 1 forms and is expected to be safe and well tolerated. Furthermore, the starting dose of this FIH study (30 ng) has a 16,000-fold safety margin compared to the NOAEL determined in a non-clinical, repeated-dose toxicity study in rabbits, where no treatment-related adverse effects were observed at the highest dose level tested, **500 μg** (125 μg/kg). In the unlikely case that the safety profile of this DM-101 dose is not as anticipated, the study will be halted because this will indicate that the tolerability of DM-101 in humans is not in agreement with what has been predicted from the non-clinical studies carried out by Desentum.

Once the safety of the single 30 ng DM-101 dose is confirmed, initiation of cohorts that include an escalating dosing regimen, according to an established rush s.c. AIT protocol will commence (cohorts 2 to 6). This is the regimen Desentum intends to pursue for pharmaceutical development. The proposed rush, “build-up”, dose escalation over 2 consecutive days has been shown to facilitate the quick desensitization of allergic patients and to allow the safe administration of high allergen doses at an early phase of treatment (Winslow, 2016). Evaluation of single, high DM-101 doses is not proposed in the study and is not considered constructive, because the safety profiles of high doses delivered by single administration versus rush dose escalation are expected to differ. Rush s.c. AIT regimens, for various aeroallergens, have been used in clinical practice for years and their safety and tolerability, compared to the prolonged dose escalation AIT protocols, has been established and found appropriate (Cox, 2006; Calabria 2013; Morais-Almeida, 2016; Winslow, 2016).

In cohort 2, the first of the dose escalation study cohorts, the starting dose will be 100 ng; this will be followed by sequential 2- or 2,5-fold dose escalation (i.e. 250 ng, 500 ng, 1,000 ng, 2,500 ng etc.) within the cohort, over 2 consecutive days. The starting DM-101 dose of 100 ng is still within the range of the starting doses employed in s.c. AIT protocols with wild-type rBet v 1 or hypoallergenic rBet v 1 products. Should the dose of 100 ng DM-101 not be found to be safe and well tolerated, as is anticipated, the study will be halted because this will indicate that the tolerability of DM-101 in humans is not as expected. The starting dose in each subsequent cohort of participants, after cohort 2 (cohorts 3 to 6), will be sequentially 2- or 2,5-fold higher than the starting dose of the preceding cohort (i.e. 250 ng, 500 ng, 1,000 ng and 2,500 ng). With this dosing scheme, the starting dose in each of the cohorts 3 to 6 will have been previously tested as the second escalation dose in the preceding cohort (Table 2).

Within each of the cohorts 2 to 6, sequential 2- or 2,5-fold dose increases are proposed to take place over 2 consecutive days (Table 2). In each of these cohorts, the maximum DM-101 dose found to be safe and well tolerated after completion of the 2 days’ dose escalation will be considered a “maintenance” dose and will be repeated on subsequent treatment visits, until the end of the treatment phase of the study. The maximum DM-101 dose proposed to be administered in the first escalation cohort (cohort 2) is 25,000 ng, which is less than the maximum dose given in s.c. AIT regimens with other Bet v 1 hypoallergens and approximately 1.6-fold higher than the maintenance dose used in s.c. AIT protocols with wild-type rBet v 1. The maximum DM-101 dose scheduled to be given in the last cohort in this FIH study (cohort 6), if safety allows it, is 500,000 ng. This dose

level is approximately 33-fold higher than the maintenance dose used in s.c. AIT with wild-type rBet v 1.

Progression from cohort 1 forward, to the subsequent cohorts, will take place only if the review of the collected safety and tolerability data from each preceding cohort is favorable (see Section 3). Dose escalation within each cohort will also take place only if safety allows it and the study's dosing discontinuation or adjustment criteria (see Section 9) have not been met.

Table 2. Originally planned Study cohorts - DM-101 Doses (ng) and Dosing Schedules* (Protocol version 1.1)

		Cohorts	1	2	3	4	5	6
Visit 2	**Day 1**	1st injection	30	100	250	500	1,000	2,500
		2nd injection	-	250	500	1,000	2,500	5,000
		3rd injection	-	500	1,000	2,500	5,000	10,000
		4th injection	-	1,000	2,500	5,000	10,000	25,000
		5th injection	-	2,500	5,000	10,000	25,000	50,000
		6th injection	-	5,000	10,000	25,000	50,000	100,000
	Day 2	1st injection	-	5,000	10,000	25,000	50,000	100,000
		2nd injection	-	10,000	25,000	50,000	100,000	250,000
		3rd injection	-	25,000	50,000	100,000	250,000	500,000
		Day 1 & Day 2 Cumulative dose	**30**	**49,350**	**104,250**	**219,000**	**493,500**	**1,042,500**
Visit 3	**Day 14**	1 injection	-	25,000	50,000	100,000	250,000	500,000
Visit 4	**Day 28**	1 injection	-	25,000	50,000	100,000	250,000	500,000
Visit 5	**Day 42**	1 injection	-	25,000	50,000	100,000	250,000	500,000
Visit 6	**Day 56**	1 injection	-	25,000	50,000	100,000	250,000	500,000
		Total Cumulative dose	**30**	**149,350**	**304,250**	**669,000**	**1,493,500**	**3,042,500**

*Acceptable Visit Windows: ±1 day for Visit 3, and ±2 days for Visits 4, 5 and 6.

1.2.3 Revised Dose Selection Rationale for Cohorts 3 and 4 (Protocol version 2.0)

Temporary halt of the study in March 2020 and interim analysis results

This study was temporarily halted because of the Covid-19 pandemic on 17th March 2020 based on PI's decision in anticipation of visit restrictions to the dosing site located at Turku University Hospital and because of the perceived Covid-19-related risks to the study subjects and study personnel. No administrations of IMP took place after that, but the follow-up of all subjects already dosed by that date was continued according to the study protocol.

By the 17th March 2020, cohort 1 dosing had been completed for all scheduled 6 subjects, and in accordance with the study protocol, the Safety Review Committee (SRC) had its first scheduled meeting and recommended the initiation of dosing in cohort 2. Dosing in cohort 2 (Visit 2) was initiated and by the time the decision to halt the study was made, 5 out of the 8 planned subjects had their scheduled Visit 2 dosing initiated. From these 5 subjects of cohort 2, only 1 subject who had received placebo completed Visit 2, Day 1 and Day 2 administration. None of the other 4 subjects who had all received DM-101 was able to complete the Visit 2 Day 1 and Day 2 administration as planned in the study protocol because of treatment-related TEAEs (Table 6 and 7). An SRC meeting took place on the 20th March 2020 to review the collected safety data at the request of the PI. The SRC recognized that although none of the pre-defined study stopping criteria were met, there were safety signals related to the rapid dose escalation regimen and recommended the discontinuation of further dosing in cohort 2 and in subsequent cohorts according to the regimen included in study protocol version 1.1. Following this recommendation, and as the study was temporarily halted, the Sponsor decided to perform an interim analysis of all available data and to open the treatment code for the subjects included in the study up to that time, in order to make an informed decision on how to amend the dosing regimen and continue the study in due time.

Table 3. Extent of exposure by subject in cohorts 1 and 2 and reasons for dose reduction and/or treatment withdrawal

Subject number	Cohort	Injection no	Dose ng (Intended*/actual)	Actual cumulative dose	Reason for dose reduction and/or withdrawal
1001	1	1	0 (Placebo)	0	
1002	1	1	30/30	30	
1003	1	1	30/30	30	
1004	1	1	30/30	30	
1005	1	1	0 (Placebo)	0	
1006	1	1	30/30	30	
2001	2	1-9	0 (Placebo)**	0	
2002	2	1	100 / 100	100	Withdrawn from the treatment after Day 1, 4th injection, due to a Grade 3 systemic allergic reaction. According to the protocol-specific dose adjustment criteria, a Grade 3 systemic reaction would have led to a dose reduction to the previous well-tolerated level, but it was considered to be in the best interest of the subject to discontinue treatment.
		2	250 / 250	350	
		3	500 / 500	850	
		4	1000 / 1000	**1850**	
2003	2	1	100 / 100	100	The subject withdrew her consent after the 6th injection of Day 1. Moreover, due to 2 grade 3 local injection site reactions following 2 injections (5th and 6th injections) the treatment would also have been stopped according to the protocol-specific treatment stopping criteria. The subject developed a Grade 2 local injection site reaction after the 5th injection that progressed to Grade 3 after the administration of the 6th injection.
		2	250 / 250	350	
		3	500 / 500	850	
		4	1000 / 1000	1850	
		5	2500 / 2500	4350	
		6	5000 / 5000	**9350**	
2004	2	1	100 / 100	100	Due to a Grade 3 local reaction after the 2nd injection of Day 1, the dose was reduced to the previous well-tolerated level (100 ng) according to the protocol-specific treatment adjustment criteria. The dosing would have continued on Day 2 with 100 ng injections, but the study was temporarily halted due to the Covid-19 pandemic and no further dosing took place.
		2	250 / 250	350	
		3	500 / 100	450	
		4	1000 / 100	550	
		5	2500 / 100	650	
		6	5000 / 100	**750**	
2005	2	1	100 / 100	100	Due to a Grade 2 systemic reaction after the 2nd injection of Day 1, , dosing was interrupted at the PI's discretion with the intention to continue dosing on Day 2 with the previous well-tolerated dose (100 ng), but the study was temporarily halted due to the Covid-19 pandemic and no further dosing took place.
		2	250 / 250	**350**	

* Planned doses of Cohort 2 included 6 injections on Day 1 and 3 injections on Day 2 of Visit 2. Only doses of administered injections are shown.
**Subject 2001 received all planned 6 injections on Day 1 of Visit 2 and 3 injections on Day 2 of Visit 2.

The interim analysis of the safety data Tables 3-7 from of the subjects included in cohorts 1 and 2 of the study (DM-101-C-001 Interim Clinical Study Report) revealed the following:

- In cohort 1, single injection of 30 ng of DM-101 was found to be safe and well-tolerated. All 4 subjects who received DM-101, but none of those 2 who received placebo, developed transient, mild, grade I local injection site reactions (mostly erythema) that disappeared within 16 h post-injection. No treatment-related systemic allergic reactions were reported.
- In cohort 2, all 4 subjects who received dosing with DM-101 on Day 1 developed treatment-related injection site reactions and 3 of them also developed systemic allergic reactions Table 4, Table 5). Specifically, the following DM-101-related systemic allergic reactions were reported during Day 1 dosing:
  a) 1 subject developed a transient Grade 2 reaction with symptoms of redness of the neck, itching of the eyes and throat, throat pain, nasal congestion, heaviness of breathing and FEV1 decrease (treated with inhaled salbutamol) after the 5th (2500 ng) and 6th (5000 ng) DM-101 injections,
  b) 1 subject developed a transient Grade 2 reaction with symptoms of generalized pruritus, urticaria with papules, angioedema of the eyelids and numbness of the lips after the 2nd (250 ng) DM-101 injection, and
  c) 1 subject developed a Grade 3 reaction with symptoms of dysphagia, angioedema, pruritus, urticaria and hypotension that peaked after the 4th DM-101 injection (1000 ng).

Most of the observed local injection site reactions were of Grade 1 or 2. Grade 3 local reactions were reported by 2 subjects. One subject developed a Grade 3 reaction (erythema) after the 2nd DM-101 injection (250 ng) and another subject developed two Grade 3 reactions (erythema and induration/swelling) after the 5th (2500 ng) and 6th (5000 ng) DM-101 injections. The reaction after the 5th injection evolved from a Grade 2 reaction to a Grade 3 reaction after the 6th injection. Overall, the starting dose of 100 ng in cohort 2 was associated with local injection site reactions that were more prominent than those seen with 30 ng in cohort 1.

None of the 4 subjects who receive dosing with DM-101 on Day 1 had Day 2 dosing initiated. In contrast, the 1 subject who received placebo completed Day 1 and 2 dosing with no TEAEs of special interest reported.

Table 4. Local injection site reactions of subjects receiving DM-101 in cohort 2

Subject Number	Injection with local reaction	Dose ng	Total dose ng	Local reaction grade
2002	1st injection	100		1
	2nd injection	250		2
	3rd injection	500		2
	4th injection	1000	1850	2
2003	1st injection	100		1
	2nd injection	250		2
	3rd injection	500		2
	4th injection	1000		2
	5th injection	2500		3*
	6th injection	5000	9350	3
2004	1st injection	100		2
	2nd injection	250		3
	3rd injection	100		2
	4th injection	100		1
	5th injection	100		2
	6th injection	100	750	2
2005	1st injection	100		2
	2nd injection	250	350	2

*This reaction progressed from Grade 2 to Grade 3 after the 6th injection had already been given

Table 5. Systemic allergic reactions of subjects receiving DM-101 in cohort 2

Subject number	Day 1 Visit 2 Actual Dose (ng)	Symptoms of systemic allergic reaction (SAR)	SAR grading
2002	1st injection: 100 ng	No	
	2nd injection: 250 ng	No	
	3rd injection 500 ng	No	
	4th injection: 1000 ng	Generalized pruritus, urticaria, angioedema in both eyelids, difficulty in swallowing, syncope, hypotension	3
2003	1st injection: 100 ng	No	
	2nd injection: 250 ng	No	
	3rd injection 500 ng	No	
	4th injection: 1000 ng	No	
	5th injection: 2500 ng	Redness of the neck, itching of eyelids	
	6th injection: 5000 ng	Itchy throat, throat pain, itching, nasal congestion, heaviness in breathing, angioedema of the eyelids, flushing, generalised pruritus, numbness, sneezing, feeling of swelling in the mouth, conjunctival erythema	2
2004	1st injection: 100 ng	No	
	2nd injection: 250 ng	No	
	3rd injection 100 ng	No	
	4th injection: 100 ng	No	
	5th injection: 100 ng	No	
2005	1st injection: 100 ng	No	
	2nd injection: 250 ng	Generalised pruritus, urticaria, angioedema of eyelids, numbness of the lower jaw and lips, increased need to swallow, conjunctival erythema	2

Total numbers of TEAES are presented in Tables 6 and 7.

Table 6. Summary of treatment-emergent adverse events in cohort 1

Category	DM-101 (N=4) f n (%)	Placebo (N=2) f n (%)	Total (N=6) f n (%)
Any TEAE	**13 4 (100.0)**	**3 2 (100.0)**	**16 6 (100.0)**
IMP-related TEAE	5 4 (100.0)	0 0 (0.0)	5 4 (66.7)
Severe TEAE	0 0 (0.0)	0 0 (0.0)	0 0 (0.0)
Serious TEAE	0 0 (0.0)	0 0 (0.0)	0 0 (0.0)
TEAE leading to discontinuation	0 0 (0.0)	0 0 (0.0)	0 0 (0.0)

Abbreviations: TEAE = Treatment-emergent adverse event; n = the number of subjects with at least one TEAE; f = the number of TEAEs

Table 7. Summary of treatment-emergent adverse events in cohort 2

Category	DM-101 (N=4) f n (%)	Placebo (N=1) f n (%)	Total (N=5) f n (%)
Any TEAE	**56 4 (100.0)**	**2 1 (100.0)**	**58 5 (100.0)**
IMP-related TEAEs	50 4 (100.0)	0 0 (0.0)	50 4 (80.0)
Severe TEAEs	0 0 (0.0)	0 0 (0.0)	0 0 (0.0)
Serious TEAEs	0 0 (0.0)	0 0 (0.0)	0 0 (0.0)
TEAE leading to discontinuation*	2 2 (50.0)	0 0 (0.0)	2 2 (40.0)

Abbreviations: TEAE = Treatment-emergent adverse event; n = the number of subjects with at least one TEAE; f = the number of TEAEs

*One of the discontinued subjects had 2 reasons for discontinuation, both withdrawal of consent and 2 Grade 3 local injection site reactions after 2 injections of IMP.

Based on the findings of the interim analysis and in order to ensure the safety of the study subjects, the dose and dose escalation scheme for further cohorts were decided to be revised.

Justification for a revision of the original dose selection rationale

The dose selection for the original protocol version 1.1 was based on starting allergen doses used in other birch pollen AIT products and the available non-clinical evidence on the allergenic potency and overall safety of DM-101.

However, direct comparison of the amounts of allergens contained in different AIT products is complicated. In addition, the quality and potency of allergen preparations depend on the particular allergen composition and purity, as well as on the formulation and stability of the product. Moreover, the fact that the potency of allergen products in Europe is expressed in manufacturer-specific units, relative to a product-specific in-house reference, further complicates any comparisons of products from different manufacturers with respect to strength and efficacy (Larenas-Linnemann 2008, Kleine-Tebbe 2019).

Prompted by the results of the interim analysis, Desentum undertook further laboratory work during the temporary halt of the clinical trial to understand the comparability of DM-101 with other marketed birch pollen products used for AIT. This work (Report DM-101-R-002) indicated that the formulation of each product may have more pronounced effects on allergen potency than originally anticipated. In all birch pollen AIT preparations used as reference materials for the initial selection of DM-101 doses for the FIH study the allergens were adsorbed on aluminium adjuvants. Aluminium adjuvants are used in vaccines to boost the immune response to the antigen, but they also provide a depot that adsorbs the antigen and prolong its release from the injection site, resulting in reduced systemic peak of allergen concentrations (Jensen-Jarolim 2015). Aluminium adjuvants may also change the conformation or even unfold the allergen (Bøgh et al. 2020). This diminishes the biological activity of the allergen, including decreased binding to IgE antibodies leading to reduced potency and hence induction of an allergic reaction. The limited comparability of adjuvanted and non-adjuvanted allergen formulations is now acknowledged. Unfortunately, no published information is available for non-adjuvanted

birch pollen allergens (or any other allergens) used for s.c. AIT that could serve as a better reference for DM-101 than the available adjuvanted products.

To investigate the effects of the aluminium adjuvant on the properties of the major birch pollen allergen Bet v 1, Desentum carried out a series of experiments (Report DM-101-R-002) where the identity, integrity and concentration of Bet v 1 in a commercially available s.c. birch pollen AIT product Alutard SQ® and DM-101 were compared. Alutard SQ is a birch pollen allergen extract adsorbed in aluminium hydroxide. Another birch pollen allergen extract product, Aquagen SQ®, which is mainly used for diagnostic purposes and does not contain aluminium hydroxide, was also included in the experiments to ascertain that the employed methods can identify the Bet v 1 protein of the comparator products correctly. Bet v 1 concentrations were measured with a commercial immunoassay and the protein integrity was analysed with SDS-PAGE and further with mass spectroscopy.

The strength of the Alutard SQ product is expressed in SQ units defined by the manufacturer. Based on the literature, 100 000 SQ-U/ml of Alutard SQ correspond to 12.3 ug/ml of Bet v 1 protein (Bødtger et al. 2002). However, the measured allergen concentration of Alutard SQ in Desentum's experiments was much lower than the expected 12.3 ug/ml, and the Bet v 1 protein or other proteins in the extract were not visible when analysed on a silver stained SDS-PAGE gel. Mass spectroscopy analyses of Alutard SQ indicate that the protein is strongly adsorbed to aluminium hydroxide, and also suggest at least partial degradation. In contrast to Alutard SQ, the concentration and integrity of both Aquagen SQ and DM-101 in Desentum's experiments were as expected. According to the literature, it is apparent that the amount of Bet v 1 present in allergen preparations has been measured before adding the aluminium adjuvant (Kaul, 2016). Thus, a likely explanation for the observed differences in the final preparations containing aluminium hydroxide is that the allergen protein is strongly adsorbed to the adjuvant and/or fragmented.

The results of Desentum's experiments suggest that in AIT preparations containing aluminium hydroxide the amount of soluble, biologically active Bet v 1 is much lower than the nominal content of Bet v 1. In contrast, the DM-101 product does not contain aluminium hydroxide and the entire antigen (rBet v 1 dm) content is soluble, intact and biologically active. Consequently, the DM-101 dose selection regimen in the original protocol version 1.1 included rapid administration of higher amounts of the antigen in active form than those used in the reference aluminium adjuvanted AIT products, a fact that may explain the unexpected occurrence of AEs indicative of allergic reactions early in the FIH clinical trial.

Revised dose selection rationale for Cohorts 3 and 4

Based on the safety findings from the initially conducted cohorts of this FIH trial and Desentum's latest laboratory data on the amount of biologically active Bet v 1 in commercially available birch pollen s.c. AIT products, it is considered important to continue this study with a DM-101 dosing scheme that carries low risk of induction of serious allergic reactions. To this end, the study design has been amended to include only 2 additional cohorts (cohorts 3 and 4) where DM-101 will be administered following a very slowly escalating repeat dose regimen, with doses starting from 30 ng, up to a maximum

of 300 ng. The rapid dose escalation over 2 consecutive days (Visit 2, Day 1 and 2) included in the original study protocol (version 1.1) has been omitted. Instead, a slow dose escalation that will take place over 5 bi-weekly dosing visits is proposed.

Dosing in both cohorts, 3 and 4, will start with administration of a single s.c. injection of placebo or 30 ng of DM-101 on Visit 2, followed by a single s.c. injection of placebo or 50 ng of DM-101 2 weeks later (Visit 3). Subsequently, in cohort 3 dosing will continue with single administration of placebo or 100 ng DM-101 on each of the Visits 4 to 6. In cohort 4, Visits 4 to 6 will include s.c. injections of placebo or increasing doses of DM-101 corresponding respectively to 100, 200 and 300 ng (Table 8). The doses of 200 ng and 300 ng will be administered as 2 and 3 s.c. injections of 100 ng respectively, with at least 30 min intervals between injections.

The starting dose of 30 ng has been selected because it was found to be safe and well-tolerated by the subjects who completed cohort 1 of this study. The subsequent 2nd dose of 50 ng and 3rd dose of 100 ng have been selected as modest steps of dose escalation in order to maximise safety. The 100 ng dose level has already been tested as the starting dose of the 4 subjects who received cohort 2 active treatment in this study; in these subjects, 100 ng DM-101 was not associated with the development of significant TEAEs or systemic allergic reactions. In cohort 3, 100 ng is the maximal planned dose that will be administered on subsequent visits until the end of the treatment phase. If this dosing scheme is well tolerated by the cohort 3 subjects, further dose escalation above 100 ng will be attempted in cohort 4 at Visit 4 (200 ng) and at Visit 5 (300 ng).

Two-week intervals between doses are considered to be long enough for the intended immunological adaptation to develop, to allow dose escalation during the treatment period. This dosing interval was also used in the nonclinical toxicology evaluation of DM-101.

Cohort 4 will not be initiated until cohort 3 Visit 2 has been completed. Dose escalation to doses above 100 ng in cohort 4 will only take place if the review of the collected safety and tolerability data from Visit 5 of cohort 3 is favourable (see Section 3). Repeated dosing and dose escalation within these cohorts will also take place only if safety allows it and the study's dosing discontinuation or adjustment criteria (see Section 9) have not been met.

Table 8 Revised Study Cohorts - DM-101 Doses (ng) and Dosing Schedules* - Protocol version 2.0

		Cohorts	1[1]	2[2]	3	4
Visit 2	**Day 1**	1st injection	30	100	30	30
		2nd injection	-	250		
		3rd injection	-	500		
		4th injection	-	1,000		
		5th injection	-	2,500		
		6th injection	-	5,000[3]		
	Day 2	1st injection	-	(5,000)[4]		
		2nd injection	-	(10,000)[4]		
		3rd injection	-	(25,000)[4]		
		Day 1 & Day 2 Cumulative dose	**30**	**(49,350)[4]**	**30**	**30**
Visit 3	**Day 14**	1 injection	-	(25,000)[4]	50	50
Visit 4	**Day 28**	1 injection	-	(25,000)[4]	100	100
Visit 5	**Day 42**	1-2 injections **	-	(25,000)[4]	100	200
Visit 6	**Day 56**	1-3 injections**	-	(25,000)[4]	100	300
		Total Cumulative dose	**30**	**(149,350)[4]**	**380**	**680**

*Acceptable Visit Windows: ±1 day for Visit 3, and ±2 days for Visits 4, 5 and 6.
** In cohort 4, doses of Visits 5 and 6 are divided into 2 and 3 injections, respectively
[1]Cohort 1 was completed according to the study protocol version 1.1
[2]Cohort 2 was started according to the study protocol version 1.1 but dosing and recruitment were interrupted at Visit 2
[3]Highest dose actually administered in cohort 2 before halt of study;
[4]Never administered

1.3. Original Risk Benefit Assessment – Protocol version 1.1

Desentum has assessed this FIH study for any risks that may be posed to the subjects taking part. DM-101 has an acceptable non-clinical safety and toxicity profile that supports initiation of clinical evaluation. Furthermore, there is preliminary, non-clinical evidence of the product's capacity to trigger lesser IgE-mediated allergic reactivity compared to rBet 1 v (DM-101 IB). Major health risks are not anticipated. However, s.c. AIT is associated with a low risk of reversible, systemic allergic reactions, mostly occurring within an hour following treatment administration (Kannan, 2013; James, 2017; Nurmatov, 2017). The use of standardized allergen extract products and rigorous practices of surveillance have made the risk for life-threatening reactions extremely small (Makatsori, 2014; Caminati,

2015). Nevertheless, the study involves risks and the potential development of local and systemic allergic reactions after dosing with DM-101 will be thoroughly monitored.

Specific risk management measures include the following:

- Only subjects in good general health and with no previous history of anaphylaxis, moderate to severe or uncontrolled asthma, or immunologic or other major disorders will participate in this study (see Inclusion/Exclusion Criteria, Section 4.2).
- The treatment phase of the study will be conducted out of the local birch pollen allergy season to reduce any potential risk from additional natural allergen exposure.
- The study will be undertaken at a clinical research unit with previous experience in FIH clinical trials and good understanding of the associated safety risks. The unit has all required facilities and knowledge how to handle medical emergencies, including severe, systemic allergic reactions, and is located very close to Turku University Hospital and its Intensive Care Unit (ICU). Dosing and over-night follow-up on Visits 2 (for all cohorts) and 3 (for cohorts 2-6) will take place within the premises of Turku University Hospital, in its Emergency Care Unit. A qualified physician will be present at the site throughout the confinement periods of the study subjects.
- The DM-101 doses proposed for evaluation have been selected based on careful consideration of the allergen doses used in various s.c. birch AIT protocols tested in the clinic (see Section 1.2.).
- Treatment administration in each dosing cohort will follow a carefully staggered schedule to assure minimal exposure to the IMP, until preliminary clinical safety data have been collected. The staggered dosing schedule for each cohort is described in detail in Section 3.2. In addition, cautious criteria have been set to stop further administration of the IMP, in case of significant AEs (see Section 9).
- The study will start with cohort 1, in which the lowest DM-101 dose will be evaluated. Subsequent progression to cohorts 2 to 6 will be sequential and will take place only after completion of the build-up phase in the preceding cohort and favorable recommendation from the study Safety Review Committee (SRC), after its review of all available safety data (see Section 3.2.).
- During the first and second dosing visits (Visits 2 and 3), all subjects will remain under close medical supervision, confined overnight in Turku University Hospital's Emergency Care unit, until completion of the 22 h - 24 h assessments after the last dose of the preceding day (see Section 3.2). During this period, a series of clinical and laboratory safety assessments will be performed. Subjects will not be discharged until the Investigator has reviewed the available safety data and finds them satisfactory. On the subsequent dosing visits (Visits 4, 5 and 6) during which no further dose escalation will take place, all subjects will remain confined in the clinical research unit for at least 4 h post-dosing. Furthermore, all subjects will be provided with detailed written instructions, rescue medication (adrenaline autoinjector) and an action plan on what to do in case of a late-appearing systemic allergic reaction.

Based on the non-clinical evidence for the reduced allergenic potential of DM-101 compared to other birch allergen products used in AIT practice, its pre-clinical safety profile and the high medical need for novel, safe, and effective forms of short-course AIT for pollen-driven allergic diseases, it is considered that the estimated risk-benefit ratio is currently appropriate for this FIH study.

1.4. Revised Risk Benefit Assessment for Cohorts 3 and 4 – Protocol version 2.0

Based on the outcomes of an interim analysis of the data collected from the subjects who participated in the first 2 cohorts of the study prior to the temporary halt due to the Covid-19 pandemic, the dose levels and dosing schemes for the subsequent dose cohorts have been revised for version 2.0 of the protocol.

Desentum has reassessed this FIH study for any risks that may be posed to the subjects. Only 2 new cohorts (cohorts 3 and 4), of similar size and composition as the originally planned 4 additional cohorts (cohorts 3-6), will be included with doses and dose escalation schemes substantially modified. The dose escalation schemes in cohorts 3 and 4 will provide information about the safety of repeated dosing on a bi-weekly basis, as well as on the development of desired immunological responses, both regarded as essential information for planning of phase II dose finding studies where the preliminary efficacy of DM-101 will be studied.

Based on the interim results from the cohort 1 and 2 subjects, transient, mild injection site reactions may occur with the doses selected for cohorts 3 and 4, but major safety risks are not anticipated. Systemic allergic reactions were reported in cohort 2, but none was reported following injection of the dose of 100 ng. Administration of doses above 100 ng per s.c. injection are not planned in the amended dosing regimen. It is acknowledged that s.c. AIT is associated with a low risk of reversible, systemic allergic reactions, mostly occurring within an hour following treatment administration (Kannan, 2013; James, 2017; Nurmatov, 2017). The use of standardized allergen extract products and rigorous practices of surveillance have made the risk for life-threatening reactions extremely small (Makatsori, 2014; Caminati, 2015). Nevertheless, the study involves risks and the potential development of local and systemic allergic reactions after dosing with DM-101 will be thoroughly monitored.

Specific risk management measures include the following:

- Only subjects in good general health and with no previous history of anaphylaxis, moderate to severe or uncontrolled asthma, or immunologic or other major disorders will participate in this study (see Inclusion/Exclusion Criteria, Section 4.2).
- The treatment phase of the study will be conducted out of the local birch pollen allergy season to reduce any potential risk from additional natural allergen exposure.
- The study will be undertaken at a clinical research unit with previous experience in FIH clinical trials and good understanding of the associated safety risks. The study team has all required facilities and knowledge how to handle medical emergencies, including severe, systemic allergic reactions, and collaborates closely with Turku University Hospital and its Intensive Care Unit (ICU). All dosing

visits of cohorts 3 and 4 will take place within the premises of Turku University Hospital, in its Emergency Care Unit. The subjects will be confined in the Unit for at least 6 h after the dosing. A qualified physician will be present at the site throughout the confinement periods of the study subjects.

- The DM-101 doses proposed for evaluation in cohorts 3 and 4 have been selected based on careful analysis of the interim results of cohort 1 and 2 subjects of this study and additional in vitro research carried out after study initiation.
- Treatment administration in each dosing cohort will follow a carefully staggered schedule to assure minimal exposure to the IMP, until preliminary clinical safety data have been collected. The staggered dosing schedule for each cohort is described in detail in Section 3.2. In addition, cautious criteria have been set to stop further administration of the IMP, in case of significant AEs (see Section 9).
- The starting dose (30 ng) of cohorts 3 and 4 has been found to be safe in the first part of this study (cohort 1). The planned dose escalation with biweekly dosing involves only very modest dose escalation. In cohort 3, all doses to be administered (30-100 ng) have already been administered as starting doses in cohorts 1 and 2 of the study without systemic allergic reactions. Progression of dose escalation above 100 ng in cohort 4 will take place only after completion of the 4th dosing of cohort 3 and favorable recommendation from the study's Safety Review Committee (SRC), after its review of all available safety data (see Section 3.2).
- Daily doses greater than 100 ng will be divided into separate injections with a dose of 100 ng in each, using at least 30 min intervals between the injections to reduce the risk of systemic allergic reactions.
- During all dosing visits, the subjects will remain under close medical supervision, confined in Turku University Hospital's Emergency Care Unit, until completion of the 6 h assessments after the last injection (see Section 3.2). During this confinement period, a series of clinical and laboratory safety assessments will be performed. Subjects will not be discharged until the Investigator has reviewed the available safety data and finds them satisfactory. The subjects' state of health will be followed up via telephone at approximately 12 and 24 h after completion of the dosing. Furthermore, all subjects will be provided with detailed written instructions, rescue medication (adrenaline autoinjector) and an action plan on what to do in case of a late-appearing systemic allergic reaction.

Based on the interim results of cohorts 1 and 2 of this study, it is considered that the estimated risk-benefit ratio is appropriate for the continuation of this FIH study according to the revised study protocol (version 2.0).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

To evaluate the safety and tolerability of s.c. administration of DM-101 in adult subjects with birch pollen allergy.

2.1.2. Secondary Objective

To determine the proportion of adult subjects with birch pollen allergy who reach the pre-defined, maximum admissible s.c. DM-101 dose in each dosing group.

2.1.3. Exploratory Objective

To evaluate the possible effects of repeated s.c. DM-101 dosing on immunological biomarkers in adult subjects with birch pollen allergy.

2.2. Endpoints

2.2.1. Primary Endpoint

The number of all Treatment Emergent Adverse Events (TEAE) in subjects receiving s.c. DM-101, compared to placebo.

2.2.2. Secondary Endpoints

The number and severity of systemic allergic reactions in subjects receiving s.c. DM-101, compared to placebo.

The number and severity of local injection site reactions in subjects receiving s.c. DM-101, compared to placebo.

The proportion of subjects reaching the pre-defined, admissible dose in each DM-101 dosing group.

2.2.3. Exploratory Endpoints

The effect of repeated s.c. DM-101 dosing on serum levels of birch allergen-specific immunoglobulins, compared to placebo.

The effects of repeated s.c. DM-101 dosing on novel, exploratory immunological biomarkers, compared to placebo.

3. STUDY DESIGN

3.1. Overview

This will be a randomized, double blind, placebo-controlled, parallel group study to evaluate the safety and tolerability of s.c. administration of DM-101 in subjects with birch pollen-evoked allergic rhinoconjunctivitis. The study will be conducted outside of the birch pollen season in Finland.

The study will include up to 4 cohorts of participants. In each cohort, subjects will be randomly allocated to receive s.c. doses of DM-101 or placebo. Subjects will be allowed to participate in only one cohort and will receive one type of treatment, with either DM-101 or placebo, throughout the study. Cohort 1 of the study included a single dose administration. Cohorts 2 to 4 include repeat dose administration.

Table 2 and 8 describes the type of dosing with DM-101 scheduled to be administered in each cohort of study participants.

The study was started with cohorts 1 and 2, and will now proceed to cohorts 3 and 4 after a substantial protocol amendment. The amended protocol version 2.0 will be followed for the conduct of cohorts 3 and 4. A previous protocol version (1.1) was followed for cohorts 1 and 2.

Dose escalation will be initiated only upon satisfactory review of all available safety data from the previous cohort(s) and favorable recommendation from the study's SRC.

An overall schematic of the study design is presented in Figure 1.

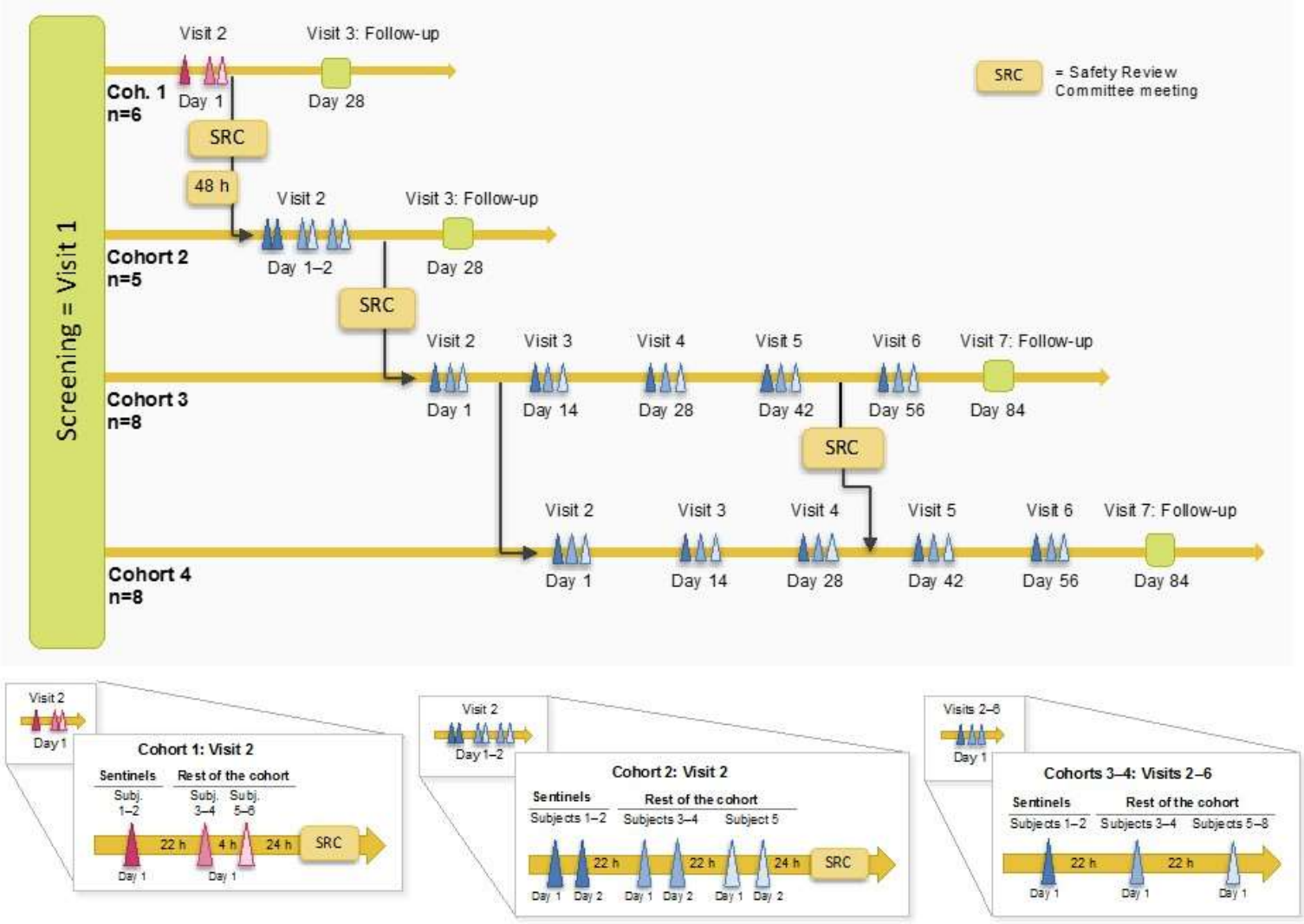

Figure 1. Overall Study Design Schematic

3.2. Study Periods

Study participation includes a screening period, a treatment period and a follow-up period.

Screening Period:

Up to 2 months (60 days) prior to treatment randomization, adult subjects with a history of birch pollen-evoked allergic rhinoconjunctivitis will be invited for screening at the clinical research unit (Visit 1). Subjects will first provide informed consent for participation in the trial and may then undergo a preliminary eligibility assessment to confirm their medical history and allergic sensitisation to birch pollen, by skin prick testing (SPT). Subjects with a positive SPT response to birch pollen will then proceed to further medical assessments to determine their eligibility in relation to the study selection criteria. At the discretion of the Investigator, screening evaluations may take place over one or two visits (Visit 1a and Visit 1b).

Treatment Period:

Once eligibility has been confirmed, subjects will proceed to the treatment period and will be randomly allocated to receive treatment with DM-101 or placebo.

Cohort 1 (completed in accordance with protocol version 1.1)

Subjects allocated into cohort 1 (Table 2) will visit the clinical research unit (Visit 2) and after a brief medical review will receive a single s.c. injection of DM-101 or placebo. All subjects in this cohort will remain confined in Turku University Hospital's Emergency Care unit until at least 24 h after dosing and will be closely monitored.

Dosing will be staggered in such a way that a sentinel group of 2 subjects, 1 receiving DM-101 and 1 receiving placebo, will be dosed first in a double-blind fashion. Treatment of the remaining subjects in the cohort will be initiated, at the earliest, 22 h after the sentinel subjects have completed their dosing, without safety findings that meet the study's stopping or treatment discontinuation criteria (see Section 9). Subjects in the main treatment group will also receive their doses in a staggered fashion, with 2 subjects receiving their doses first and the remaining subjects being dosed no sooner than 4 h later.

Cohort 2 (started in accordance with protocol version 1.1, discontinued, not to be re-started)

Initiation of cohort 2 was to take place only after completion of all Visit 2, 24 h post-dosing assessments in all subjects of cohort 1, review of all safety and tolerability data and a favorable recommendation from the study's SRC. There was to be an at least 2 days' interval between completion of the post-dosing 24 h monitoring period in cohort 1 and initiation of dosing in cohort 2.

The study was temporarily halted because of the Covid-19 pandemic after completion of Visit 2 for 1 subject and partial completion of Visit 2 for 4 subjects. Because of the reporting of TEAE of local and systemic allergic reactions in 4 of the 5 participants, the SRC recommended that dosing in the study should not be re-started without a substantial protocol amendment.

VISIT 2

According to version 1.1 of the study protocol, subjects allocated into cohort 2 (Table 2) were to enter Turku University Hospital's Emergency Care unit and after a brief medical review receive a series of s.c. injections with escalating doses of DM-101 or placebo over 2 consecutive days (Visit 2 Day 1 and Visit 2 Day 2). All subjects in cohort 2 were to remain confined overnight in the hospital and were to be closely monitored until at least 24 h following completion of dosing on Day 2.

Dosing and dose escalation was to be staggered in such a way that 2 sentinel subjects, 1 receiving DM-101 and 1 receiving placebo, were to be dosed first in a double-blind fashion. Dosing of the remaining subjects in the cohort was to be initiated, at the earliest, 22 h after sentinel subjects had completed their Day 2 dosing, without safety findings that would meet the study's stopping or treatment discontinuation criteria (see Section 9). Subjects in the main treatment group were also to receive their doses in a staggered fashion, with 2 subjects starting first to receive doses and the remaining subjects starting to receive doses no sooner than approximately 22 h after the first two subjects of the main group had completed their Day 2 dosing.

Treatment on Day 1 was to start with administration of 100 ng of DM-101 or placebo. This was to be followed by administration of progressively escalating doses of DM-101 or placebo, at approximately 30 min intervals, up to a total of 6 s.c. injections per subject/day. On Day 2, treatment was to start with a repeat of the top DM-101 dose administered on Day 1 or placebo, followed by another 2 administrations of escalating DM-101 doses or placebo, approximately 30 min apart, up to a maximum of 3 s.c. injections per subject/day. Dose escalation, in each subject, was to be allowed only if the study's stopping and treatment discontinuation-adjustment criteria were not met (see Section 9).

VISITS 3-6

Dosing on Visit 3 was to take place only if there was a favorable recommendation from the SRC, after reviewing of all safety data collected from Visit 2 (Day 1 and Day 2).

The subjects were to return to the hospital 2 weeks (± 1 day) after completion of their Visit 2 Day 2 treatment (Visit 3), and after a brief medical review were to receive a single s.c. injection of the last DM-101 dose they were administered on Visit 2 Day 2 (Day 2 injection 3) or placebo. The subjects were to remain confined overnight in Turku University Hospital's Emergency Care unit and were to be discharged only after satisfactory medical review by the attending physician of the clinical research unit, no sooner than approximately 24 h after dosing.

After Visit 3, dosing was to be allowed only if the study's stopping and treatment discontinuation criteria had not been met on the previous dosing visit (see Section 9).

The subjects were to return to the clinical research unit for another 3 visits (Visit 4, Visit 5 and Visit 6). Visit 4 was to take place 2 weeks (± 2 days) after Visit 3, followed by Visit 5 and Visit 6, each after another 2 weeks' (± 2 days) interval. On each of these visits, subjects were to receive, after a brief medical review, a single s.c. injection of DM-101 or placebo. The dose of DM-101 each subject was to receive was to be the same as that administered on Visit 3. On each of these visits, the subjects were to remain confined in the clinical research

unit for approximately 4 h after dosing and were to be discharged only after satisfactory medical review by the attending study physician. All subjects were to receive a phone call from the clinical research unit, approximately 24 h after discharge, for a brief medical update.

On each of the visits 3 - 6, the sentinel subjects of each cohort were to receive dosing first. The remaining subjects were to receive dosing at least 22 h later. Subjects in the main group were also to receive dosing in a staggered fashion, in such a way that there was to be an at least 30 min interval between each injection.

Cohorts 3 and 4

The revised dosing scheme of protocol version 2.0 will be applied in these cohorts (cohorts 3 and 4). There will be 6 subjects in each cohort allocated to receive s.c. injections of DM-101 and 2 subjects allocated to receive corresponding placebo injections. The recruitment procedures and subject selection criteria have not been modified for version 2.0 of the study protocol.

VISIT 2

Subjects allocated into cohorts 3 and 4 (Table 8) will enter Turku University Hospital's Emergency Care unit, and after a brief medical review and other eligibility assessments they will receive a single s.c. injection of 30 ng of DM-101 or placebo. The subjects will remain confined in the hospital for approximately 6 h following dosing.

Dosing will be staggered in such a way that 2 sentinel subjects, 1 receiving DM-101 and 1 receiving placebo, will be dosed first in a double-blind fashion. Dosing of the remaining subjects in the cohort will be initiated no sooner than 22 h after the sentinel subjects have completed their Visit 2 dosing, without safety findings that would meet the study's stopping or treatment discontinuation criteria (see Section 9). Subjects in the main treatment group in each cohort will also receive treatment in a staggered way, with 2 subjects starting first to receive doses and the remaining subjects starting to receive doses no sooner than approximately 22 h after the first two subjects of the main group have received their Visit 2 dosing.

Visit 2 of cohort 4 subjects will take place after Visit 2 of cohort 3 has been completed.

VISITS 3-6

After Visit 2, dosing in each cohort will be allowed only if the study's stopping and treatment discontinuation criteria have not been met on the previous dosing visit (see Section 9).

All subjects will return to the hospital for another 4 visits (Visit 3, Visit 4, Visit 5 and Visit 6) on a biweekly basis for the subsequent dosings. In cohort 3, subjects will receive a single s.c. injection on each of these visits. In cohort 4, subjects will receive a single s.c. injection on Visits 3 and 4 and a series of 2 or 3 s.c. injections on Visits 5 and 6, respectively, with a minimum of 30 min interval between subsequent injections. Each injection will be given at a slightly different site of the exterior surface of the upper arm. The injections will alternate between the right and left arm.

Dose escalation to the 200 ng daily dose (Visit 5) in cohort 4 will only take place after a favourable recommendation from the SRC, once it has reviewed all available safety data so far collected in the study, including data from Visit 5 of cohort 3.

On each of the Visits 3-6. dosing will be staggered in the same way as on Visit 2, ie. 2 sentinel subjects, 1 receiving DM-101 and 1 receiving placebo, will be dosed first in a double-blind fashion. Dosing of the remaining subjects in the cohort will be initiated no sooner than 22 h after the sentinel subjects have completed their dosing, without safety findings that would meet the study's stopping or treatment discontinuation criteria (see Section 9). Subjects in the main treatment group in each cohort will also receive treatment in a staggered way, with 2 subjects starting first to receive doses and the remaining subjects starting to receive doses no sooner than approximately 22 h after the first two subjects of the main group have received their dosing.

Follow-up Period:

All subjects will return to the research site for a Follow-up visit (Visit 3 for cohort 1 and Visit 7 for cohorts 2-4), for medical assessment and collection of blood samples. The Follow-up visit will take place approximately 4 weeks (28 days ± 3 days) after the last dosing of each subject.

3.3. Safety Review Committee

For this study, a SRC has been assembled. After completion of cohort 1 and cohort 2 and the interim data analysis, the SRC is responsible for 1) providing recommendations on the dose escalation from 100 ng to 200 ng in cohort 4 based on the safety data collected up to and including cohort 3 Visit 5 and cohort 4 Visit 4, i.e. prior to cohort 4 Visit 5, where the administration of 200 ng dose is planned; 2) on continuation of dosing of cohort 3 to Visit 6; 3) on continuation or termination of the study; 4) on possible suspension or modification of dosing based on the study's stopping criteria (see Section 9); 5) on the appropriateness of the safety measures and the possible need for alterations. If needed, the study will be halted until appropriate measures have been taken to amend the study protocol and until all relevant approvals have been received to continue the study.

Additional SRC meetings will be held, as needed; additional meetings will be triggered by safety observations as described in Section 9.

The SRC includes members with experience in the conduct and risk assessment/management of clinical trials and ethical aspects. The SRC is comprised of the Principal Investigator, the Sponsor's Medical Monitor, representative(s) of the Sponsor and a qualified biostatistician.

Detailed instructions for SRC meetings and its decision-making process are described in a separate document called "SRC Instructions". The study data will be reviewed blinded. However, if it is deemed necessary for ascertaining the safety of the study subjects, the review may also be unblinded.

4. STUDY SUBJECTS

4.1. Number of Subjects

An adequate number of subjects, with documented birch pollen allergy, will be enrolled in the study, such that up to 27 subjects will be randomized to receive treatment with IMP in the scheduled 4 cohorts of participants. In particular, in:

Cohort 1: 6 subjects were randomized in a ratio of 2:1 to receive single doses of DM-101 or placebo.

Cohort 2: 5 subjects were randomized to receive repeated doses of DM-101 or placebo before the temporary halt of the study. Because of systemic allergic reactions observed in 3 of the 5 thus far included participants on Day 1 of Visit 2, the SRC did not recommend re-start of dosing in cohort 2 without a substantial protocol amendment. Four of the 5 enrolled subjects had received DM-101 on Visit 2 and one subject had received placebo injections.

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

For replacement of cohort 3 and 4 subjects who prematurely discontinue the study for reasons other than TEAE, additional subjects may be enrolled at the discretion of the Investigator, following discussion and agreement with the Sponsor.

4.2. Eligibility Criteria

Subjects will be eligible for inclusion in this study only if all of the following criteria apply:

4.2.1. Inclusion Criteria

1. Males or females, aged 18 to 65 years inclusive.

2. Good general health, as determined by the Investigator, based on medical evaluation, including medical history, physical examination, laboratory tests and electrocardiogram (ECG).

3. A documented clinical history of birch pollen-induced allergic rhinitis or rhino-conjunctivitis with symptoms that interfere with daily activities or sleep and remain bothersome despite the use of relevant symptomatic medication, and have been present over, at least, 2 allergy seasons.

4. Bet v 1 specific serum IgE ≥ 0.7 kU/L (class 2), measured by ImmunoCAP®.

5. Positive SPT to birch pollen allergen, with a wheal diameter ≥ 5 mm (average of longest and orthogonal) greater than that produced by the negative control.

6. Body weight ≥50 kg and body mass index (BMI) within the range 18–35 kg/m^2.

7. Females are eligible to participate only if they are of:

- non-childbearing potential, defined as pre-menopausal females with documented tubal ligation or hysterectomy, or postmenopausal, defined as 12 months of spontaneous amenorrhea (in questionable cases a blood sample with levels of follicle stimulating hormone (FSH) > 40 MIU/ml and estradiol < 40 pg/ml (<147 pmol/L) is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods in Section 4.3.1.1. if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks should elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume the use of HRT during the study without the need to use a contraceptive method.
- child-bearing potential and have a negative serum pregnancy test result at Screening and a negative serum pregnancy test result within 10 days prior to the first dosing visit, a negative urine pregnancy test before each subsequent dosing and agree:
- to use one of the contraception methods listed in Section 4.3.1.1. starting at least 2 weeks prior to the start of dosing to sufficiently minimize the risk of pregnancy during the treatment period of the study. Female subjects must agree to use contraception until 30 days after the last treatment administration.
- or abstains from sexual intercourse or has only same-sex partner(s), when this is her preferred and usual lifestyle.

8. Males who are sexually active with a female partner of childbearing potential must agree to use one of the contraception methods listed in Section 4.3.1.2.

9. Willing and able to provide written informed consent.

10. Willing and able to comply with the study requirements.

4.2.2. Exclusion Criteria

1. History or findings on physical examination of any significant disease or disorder (e.g. cardiovascular, pulmonary, gastrointestinal, hepatic, renal, neurological, immunological, musculoskeletal, endocrine, metabolic, major psychiatric, major physical impairment, cancer) which, in the opinion of the Investigator, may put the subject at risk because of participation in the study, influence the results of the study or the subject's ability to participate in the study.

2. Current diagnosis of asthma (other than seasonal during the birch pollen allergy season), requiring Global Initiative for Asthma (GINA) Step 2 or higher treatment, or asthma partially controlled or uncontrolled according to GINA classification in the 6 months before Screening.

3. History of asthma deterioration that resulted in emergency treatment or hospitalisation in the 12 months before screening, or a life-threatening asthma attack (e.g. one requiring intubation and mechanical ventilation) at any time in the past.

4. Forced Expiratory Volume in one second (FEV_1) < 70% of predicted, regardless of asthma status at screening or baseline assessment at the first dosing visit.

5. History of severe drug allergy, severe angioedema or systemic allergic reaction of Grade 3 or greater, according to the World Allergy Organization (WAO) scale, due to any cause.

6. Use of systemic glucocorticoid medication within 30 days prior to Screening.

7. Use of anti-IgE medication within 3 months prior to Screening.

8. Use of mast cell stabilisers, anti-leukotriene agents or anti-histaminics less than 1 week prior to dosing initiation.

9. A course of short-duration allergen-specific immunotherapy or more than 3 months' treatment with long-duration allergen immunotherapy, within five years prior to Screening.

10. History of intolerance to the study drug, rescue medications (i.e. adrenaline, antihistaminics, glucocorticoids), or their excipients.

11. Regular use of angiotensin-converting enzyme inhibitors, beta-adrenergic blockers or monoamine oxidase inhibitors.

12. Ongoing treatment with substances interfering with the immune system.

13. Treatment with an investigational drug within 30 days prior to Screening or concurrent participation in another clinical trial.

14. Contraindication for the administration of adrenaline (e.g. subjects with acute or chronic symptomatic coronary heart disease or severe hypertension).

15. Significant history of alcohol or drug abuse in the past 5 years, or a positive Screening or pre-dose drug/alcohol test result. A positive screening result for benzodiazepines or opioids may be accepted at the discretion of the investigator, if the finding can be satisfactorily explained by the subject's medical history and concomitant medication information.

16. Females who are pregnant, lactating or planning to become pregnant, or plan to donate oocytes for *in vitro* fertilisation during the study treatment period or within 30 days following the treatment period. Subjects unwilling to employ appropriate contraceptive measures to ensure that pregnancy will not occur either during or for 30 days following the completion of the treatment period.

4.3. Lifestyle and Dietary Restrictions

4.3.1. Contraception Requirements

4.3.1.1. Female Subjects

Women of childbearing potential (WOCBP) and females on hormone replacement therapy (HRT) whose menopausal status is in doubt should use a contraceptive method with a failure rate of < 1 %. These may include oral, transdermal or injectable contraceptives, intrauterine devices or barrier methods (diaphragms, condoms, spermicides), practicing abstinence or a non-heterosexual lifestyle or having male partners who are sterile (e.g. vasectomised for at least 90 days).

During the study, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant.

4.3.1.2. Male Subjects

Male subjects with WOCBP sexual partners must use an effective contraceptive method from the day of the first administration of study treatment until the Follow-up visit. Effective contraceptive methods include the use of a latex condom plus the use by the female partner of a highly effective contraceptive method (see Section 4.3.1.1.). Periodic abstinence (e.g. calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.3.2. Meals and Dietary Restrictions

Subjects will be required to be fasting for 2 h pre- and post-treatment administration, for reasons of safety. Intake of small amounts (<2 dl) of water will be allowed.

4.3.3. Caffeine, Alcohol, Recreational Drugs and Tobacco Use

Subjects will have to abstain from ingesting excessive amounts (more than one cup) of caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, chocolate) for 6 h prior to each treatment administration.

Subjects will have to abstain from alcohol for 24 h prior to each visit to the clinical research unit and until collection of all assessments has been completed.

Use of tobacco products is not allowed during the stay in the clinical research unit.

Subjects should refrain from all recreational drugs from screening until the end of the Follow-up period.

4.3.4. Exercise, blood donation and vaccinations

Subjects will have to abstain from strenuous physical exercise for 48 h prior to each blood collection for clinical laboratory tests.

Subjects will be asked to refrain from donating blood for purposes not related to this study or receiving any immunization from the Screening visit until the end-of-study visit.

4.4. Subject Withdrawal and Procedures

A subject may withdraw from the study at any time at his/her own request and for any reason. Possible withdrawal of consent will not have any negative effect on the subject's medical care.

When a subject chooses to withdraw from the study, the Investigator will record, where possible, a reason according to the following:

- Treatment related adverse effects
- Unpleasant study procedures
- Another disease or condition that intervenes and prevents continuation in the study
- External factors unrelated to the study

A subject may also be withdrawn by the Investigator for the following reasons:

- Adverse events which in the opinion of the Investigator compromise the subject's participation in the study
- Non-compliance with study procedures
- Lost to follow-up
- Withdrawal of consent
- Protocol violation
- Termination of the study
- Pregnancy prior to completion of planned dosing of the IMP
- The subject cannot comply with study requirements
- Use of any prohibited medication during the study

For subjects who withdraw from the study, all safety assessments scheduled for the Follow-up visit will be requested and observations will be recorded as far as possible. Reasons for omission of tests will be documented. The date and reason(s), if provided, for withdrawal from the study will also be recorded in the electronic Case Report Form (eCRF).

If the subject withdraws due to an AE, all of the Follow-up assessments will be requested and the event followed until resolution or care is transferred to the subject's general practitioner or primary care physician.

It will be decided case-by-case whether a discontinued subject will be replaced or not. Discontinued study subjects are not allowed to re-enter the study. Replacement procedures are briefly described in section 4.1.

4.5. Screening and Baseline Failures

From subjects screened but not included in the study, the following data will be collected on eCRFs: date of Informed Consent, demographic information, the inclusion/exclusion criterion/criteria causing the exclusion and the date of the decision of exclusion.

4.6. Subject Completion

A completed subject is one who has completed all phases of the study including the Follow-up visit.

The end of the study is defined as the last subject's Follow-up visit (Visit 3 for cohort 1 or Visit 7 for cohorts 2 to 4).

4.7. Study Extension - Optional Sub-Study

An extension of the study to include an additional follow-up visit after the birch pollen allergy season of 2021, for information on allergic symptoms and blood sample collection for the assessment of immunological biomarkers, may be considered for the subjects participating in cohorts 2-4, if the results of the core study, conducted prior to the birch pollen allergy season of 2021, are satisfactory. Participation in this sub-study will be optional and based on separate consent.

5. STUDY MEDICATIONS

5.1. Investigational Medicinal Products

The active Investigational Medicinal Product (IMP) of the study is DM-101.

DM-101 is a s.c. AIT product presented as a solution for s.c. injection. The active substance is a genetically engineered, purified, recombinant protein derived from the major birch pollen allergen Bet v 1.

The drug product of the IMP, DM-101 is a sterile solution.

The placebo product in this study is the diluent for DM-101.

The IMP DM-101 and placebo have identical appearance. The solution is colorless or slightly yellow, and clear or opalescent.

5.1.1. Route of Administration

Both IMPs, DM-101 and placebo, will be administered by s.c. injection.

5.1.2. Labelling and Packaging

The DM-101 drug product is filled into 2R Ph.Eur. Type I clear glass vials in 2.2 ml volume. The vials are closed with Fluorotec stoppers and aluminium seals.

The diluent for DM-101 is filled in 15 ml Ph.Eur. Type I glass vials in 10 ml volume. The vials are closed with bromobutyl stoppers and aluminium seals.

Individual study medication vials and study packs will be labelled in accordance with applicable Good Manufacturing Practice (GMP) regulations. The vial label will record the study identifier, product name, batch number, sponsor's name, as well as the subject and visit number/date, which will be filled in by the study site personnel before use. The DM-101 vials will be packed in carton boxes of 10 vials and the diluent vials will be packed in carton boxes of 10 vials. The outer packaging of each box will contain the following information: study identifier, product name, strength, dosage form, route of administration, quantity of vials, investigator's name, name and address of sponsor, batch number, period of use, storage conditions, "for clinical trial use only".

5.1.3. Manufacturing

The DM-101 drug product and the diluent for DM-101 are manufactured by Biovian Oy, Turku, Finland, in accordance with current EU Good Manufacturing Practice, at appropriately licensed facilities.

5.1.4. Storage and Handling Procedures

IMPs will be stored refrigerated at + 2- +8 °C in a designated storage area at the clinical research unit, in a secure, temperature controlled, locked environment with restricted access.

No preservative is used in the drug product. Therefore, each vial is for single use only.

The Sponsor will be permitted, upon request, to audit the supplies, storage, dispensing procedures and records, provided that the blinding of the study is not compromised.

5.1.5. Accountability

In accordance with Good Clinical Practice (GCP), the clinical research unit will be accountable for all supplies of DM-101 and placebo. Details of receipt, storage, reconstitution, administration and return will be recorded.

All unused supplies of DM-101 and placebo will either be destroyed at the clinical research unit or returned to the Sponsor at the end of the study, in accordance with instructions by the Sponsor.

5.1.6. Dosage and Administration

5.1.6.1. Reconstitution and Handling of Investigational Medicinal Product

The reconstitution process includes dilution of the DM-101 drug product with Diluent to DM-101 and extraction of the required volume of the IMP into a sterile syringe for s.c. administration.

All steps included in drug IMP reconstitution will be performed at the clinical research site under aseptic conditions (under a laminar flow hood), using sterile equipment, suitable for preparing sterile injection solutions for human use by clinical research unit personnel who are not otherwise involved in the study.

3 serial dilution steps are required to reach the desired dose/concentration of DM-101 for cohorts 3 and 4 according to protocol version 2.0.

All dilution vials used in the reconstitution will be labelled with the dilution level, subject identifier and preparation date.

The reconstitution process will be performed according to a separate *"Instructions for Reconstitution and Handling of Study Products"* manual.

The personnel preparing the drug IMP doses must know the treatment code (active or placebo). Therefore, to protect the double-blind administration, according to the study design, this process will be performed by designated unblinded clinical research unit personnel who will not be otherwise involved in the study. The filling of the injection syringe will be done by the unblinded personnel preparing the dilutions. Study personnel administering the injections (blinded) to the subjects will receive the pre-filled injection syringes labelled with subject number and injection number and will adjust the volume in the syringe to the final dose volume right before the injection, thus they will be blinded to the actual treatment allocation. The administered volumes of the active product and placebo will be identical at each dose level, to allow double-blind administration.

5.1.6.2. Administration for Cohorts 3 and 4

On the Dosing Visits, the IMP will be administered after a brief medical review that includes the procedures described in Table 11, to confirm the eligibility of the subjects. Abnormal findings may require suspension of dosing (see Section 4.2). The Investigator should discuss any findings of concern with the Medical Monitor before dosing.

The person administering the injection (blinded) will adjust the volume in the syringe to the final dose volume right before the injection. The injection will be administered s.c. by the Investigator or designee into the exterior surface of the upper arm. On Visits 5 and 6 in cohort 4 where several s.c. injections are scheduled, the injections will be administered in alternate arms (right - left - right).

The doses will be administered using a 1 mL sterile syringe and an appropriately sized needle (25 G). The injection technique follows standard AIT practices, with aspiration to ensure extravascular needle placement and slow injections.

The administered injection volume will vary from 0.03 to 0.1 ml (Table 9) depending on the dose. In each cohort of participants, for each IMP administration, the volume for injection of placebo will be equal to the active product volume for injection.

Table 9 Cohort 3 and 4: DM-101 dilution level and concentration, injection volume and number of injections / dose

Dose (ng)	Dilution level	Concentration of the dilution	Number of injections	Volume/injection (ul)
300 *	1:1 000	1000 ng/ml	3	100*
200 **	1:1 000	1000 ng/ml	2	100**
100	1:1 000	1000 ng/ml	1	100
50	1:1000	1000 ng/ml	1	50
30	1:1 000	1000 ng/ml	1	30

* Dose 300 ng consists of 3 injections of 100 ul volume each
** Dose 200 ng consists of 2 injections of 100 ul volume

The subjects will be in a sitting/supine position during the injections. Subcutaneous dose volumes varying from 0.03 to 0.10 ml (Table 9) will be injected per injection. In cohort 4, the total dose volume of 2 and 3 injections at Visits 5 and 6 will be 0.2 and 0.3 ml, respectively.

Subjects will be dosed using a sentinel strategy as described in Section 3.2. The doses of DM-101 scheduled to be administered in each cohort are presented in Table 8.

5.2. Treatment Assignment

At the Screening visit, after signing of the ICF (Informed Consent Form), potential study participants will be assigned unique, individual screening numbers starting from S001. After confirmation of eligibility, at admission, subjects will be assigned subject numbers in the order in which they will be enrolled in the study, as shown in Table 10. The subject number will determine the allocation of participants into the 4 study cohorts.

Table 10 Assignment of Subjects to Cohorts for Treatment Allocation

Cohort	Subject Numbers
1	1001-1006
2	2001-2008
3	3001-3008
4	4001-4008

If applicable, replacement subjects in cohorts 3 and 4 will receive the same cohort and treatment allocation as the subjects they replace. Replacement subjects will be allocated the same subject number as the replaced subject with the addition of number 1 at the beginning (e.g. if subject number 3001 is replaced, the replacement subject's number will be 13001).

5.3. Randomization and Blinding

This is a double-blind study. The site personnel and the study subjects will know the dose level(s) of DM-101 under investigation in each cohort of participants but will be blinded to the

type of treatment (active or placebo) allocated to an individual subject. The blinding of the IMP will be achieved by employing an unblinded member of the study team to prepare the injection syringes for dosing of placebo and active product at each DM-101 dose level of each cohort.

Allocation to treatments will be according to a predetermined random order resulting from block randomization with randomly permuted blocks. Randomization will take place for each cohort separately. 4Pharma Ltd. will generate the randomization list using the statistical analysis system SAS® for Windows and its PROC/Plan procedure.

The randomization list will be provided to the designated person at the clinical research unit who will be responsible for the handling of the IMP. To keep the study double-blind, this person will not participate in any other study activities. The person who will prepare the IMP for injection to the study participants must be a qualified health care professional.

The randomization according to the randomization list is implemented in the electronic data capture (EDC) system, and the subjects in each cohort will be randomly allocated to treatments by the Investigator.

5.4. Breaking of the Blinded Codes

For cases of emergency, the Investigator or the persons to whom emergency unblinding have been delegated are provided with an electronic unblinding function in the EDC system to break the randomization code for a single subject. In addition, sealed subject-specific emergency code envelopes containing the treatment allocation for each subject in separate envelopes are available to ensure that unblinding can be performed at any time needed.

In case the emergency envelope is used for unblinding the study treatment for an individual subject, the reason for unblinding has to be written on the envelope. In addition, the person performing the unblinding has to date and sign the envelope. The code must not be broken for any other reason than a medical emergency.

The randomization code of cohort 1 and 2 subjects was broken for an interim analysis after the study had been temporarily halted and the database for cohort 1 and 2 subjects had been locked. The blinded randomization code for all cohort 3 and 4 subjects will be broken only after all subject data have been recorded and verified, and the database has been locked.

5.5. Procedures for Monitoring Subject Compliance

When each dose of IMP is prepared for a subject, the preparation of the dose will be confirmed by a second unblinded member of the clinical research unit staff. The study medication will be administered by s.c. injection by the Investigator or designee. There will be close medical supervision during and after treatment administration.

The date and time of each administered dose will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of treatment administration by a member of the clinical research unit staff, other than the person administering the study treatment.

5.6. Concomitant Treatments

The Investigator must record the use of all concomitant medications, both prescribed and over-the-counter, into the eCRF and the subject's medical records. This includes medications used on both regular and as-needed basis.

5.7. Permitted Medications

Any concomitant medication will be considered on a case by case basis, by the Investigator and the Medical Monitor. Paracetamol up to 4 g/day will be permitted as required, at the discretion of the Investigator. Hormonal contraceptives may be used by WOCBP. No medication will be allowed during the confinement of the subject in the clinical research unit, without approval by the Investigator. In an emergency, the Investigator may administer any necessary medication, as considered appropriate.

Two adrenaline autoinjectors will be provided by the clinical research unit at Visit 2 to all subjects participating in cohorts 3 and 4, for use at home in case of a delayed allergic reaction. Detailed written instructions and an action plan on what to do in case of a delayed, systemic allergic reaction will also be provided (Appendix 2).

5.8. Prohibited Medications

Subjects must abstain from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first administration of study medication and until completion of the Follow-up visit, unless in the opinion of the Investigator (in consultation with the Medical Monitor, if needed) the medication will not interfere with the study.

Oral antihistamines and local application of glucocorticoids on the skin should not be used for 5 days prior to SPT, at Screening.

Use of the following medications is not permitted during the study, prior to completion of dosing:

- Monoamine oxidase inhibitors (14 days minimum washout period prior to initiation of dosing)
- Beta-adrenergic blockers (7 days minimum washout period prior to initiation of dosing)
- Angiotensin-converting enzyme inhibitors (7 days minimum washout period prior to initiation of dosing)

Subjects using any of the above medication during the study will be withdrawn from treatment administration.

5.9. Non-Drug Therapies

Subjects must abstain from taking any vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug is a potential enzyme inducer) prior to the first administration of

study medication until completion of the Follow-up visit, unless in the opinion of the Investigator the medication will not interfere with the study.

5.10. Treatment of Study Treatment Overdose

For this study, any dose of DM-101 exceeding the dose levels described for each cohort in Table 8, will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose. The Investigator will use clinical judgment to treat any overdose, if and as needed.

6. STUDY CONDUCT FOR COHORTS 3 AND 4

6.1. Recruitment

Adult subjects with a history of birch pollen-driven allergic rhino-conjunctivitis will be invited by the clinical research unit to participate in the study.

The contract research organization (CRO) performing the study, CRST, has a data bank of potentially eligible subjects who may be invited for participation in the study.
Subject recruitment may additionally be carried out by advertisements in public media. The texts to be used in recruitment advertisements and a description of other possible means of subject recruitment will be included in the clinical trial submission to the Ethics Committee (EC).

Subjects potentially interested in participating in this study will contact the CRO staff (e.g., Study Nurse, Investigator) via the contact information included in the recruitment advertisements, i.e. phone, e-mail or other means. At the initial contact, a dedicated member of staff will brief all potential study participants, in layman's language, about the overall study objectives, general time requirements for participation and eligibility criteria. All potential candidates will be told, at the beginning of the communication with the CRO staff, that the information gained in this initial contact will be collected on a study-specific interview form to be included in the study file. The name, date of birth and contact information of the subject will be recorded on the interview form. The collection of personal information is described in a Description of the Personal Data Register, which is kept in the Investigator Site File (ISF) and is made available to the subjects, if they wish. If a subject candidate does not decide to participate in the study, his/her personal information will be destroyed confidentially when the study file is archived.

During this initial contact, a preliminary evaluation of the key inclusion and exclusion criteria of the trial will be performed and recorded in the interview form. If the main eligibility criteria are not fulfilled, the subject will be immediately told and the interview will be terminated with possible health-related instructions. If the subject is found to be a suitable candidate for participation in the study, the procedures for providing the written ICF will be discussed, and upon the subject's wish, a screening visit may be booked.

Recruitment of subjects will start after approvals for the conduct of the clinical trial have been received from the EC and CA (Competent Authority).

6.1.1. Study Subject Screening Log and Identification Log

The investigator will keep a subject identification list in the ISF. The list includes information to link all study-related records to a subject, i.e. source data. Furthermore, a subject screening and enrolment log of all subjects screened for the study will be maintained. The identity of the subject (screening number, the subject's first name, last name and personal identity number), date of ICF, date of entry into the study or date of exclusion and the reason for exclusion, if applicable for those recruited for screening but not fulfilling the eligibility criteria, will be recorded on the list.

6.2. Screening

Visit 1 (Visit 1a and 1b)

Subject candidates interested in participating in the study and potentially eligible will undergo screening assessment to define their eligibility. Screening will be performed up to a maximum of 60 days before randomisation and may consist of 2 visits to the clinical research unit (Visit 1a and Visit 1b).

At the first screening visit, prior to any study procedures taking place, information about the study will be given, both verbally and in writing, and written ICF must be obtained from each subject. The provided study information will explain the objectives of the study and its potential risks and benefits. All subjects must have adequate time to read the provided information and to ask the Investigator any questions they may have. The Investigator must be satisfied that each subject has understood the information provided, before written consent is obtained. If there is any doubt as to whether the subject has understood the written and verbal information, the subject must not enter the study.

If a subject agrees to participate, he/she will be asked to sign and date an ICF. The original signed ICF will be kept in the ISF and must be made available for inspection by the Sponsor or representatives of a regulatory authority. A copy of the signed ICF will be given to the subject. A record must also be made in the medical records that the subject voluntarily agreed to participate in the study.

After informed consent is obtained, the Visit 1 procedures described in Table 11 (for cohorts 3 and 4) will take place (see Section 6.5.).

During screening, the SPT will be performed before the collection of a blood sample for birch pollen-specific IgE measurement. Only subjects with a positive response to birch pollen allergen in the SPT, as defined by the study's eligibility criteria (see Section 4.2), will proceed to blood sample collection for assessment of their birch pollen-specific IgE. The screening SPT may be rescheduled, if the subject has taken oral antihistaminics and/or applied glucocorticoids to the skin in the previous 5 days.

Pregnancy testing from serum for WOCBP should be performed at screening and be

additionally arranged for 10 days prior to the first treatment visit (Visit 2) according to the eligibility criteria, if the interval between the 2 visits is longer.

Subjects who failed screening should not be rescreened for participation in the study.

6.3. Treatment Period

The treatment period will start out of the birch pollen season of the region where the clinical research unit is located.

At least 7 days after completion of screening, eligible subjects will enter into the study's treatment period, where they will be allocated into cohorts 3 or 4 of participants. Upon confirmation of eligibility, study subjects will be given participant cards stating that they are participating in a clinical trial, their subject number and the Investigator's 24-hour contact numbers.

All WOCBP participating in the study must have a serum pregnancy test performed no earlier than 10 days prior to Visit 2, and a urine pregnancy test performed prior to dosing on each subsequent treatment visit. The pregnancy test must be negative for the subject to be dosed.

Dosing will take place by s.c. injection of DM-101 or placebo on the exterior surface of the upper arm.

All dosing visits of cohorts 3 and 4 will take place in Turku University Hospital's Emergency Care Unit, with confinement until 6 h after completion of dosing. At all visits, emergency equipment, including a cardiac resuscitation trolley, equipment for airway insertion, oxygen cylinders, portable suction machines, defibrillator, circulation lines, and drugs must be available and immediately accessible for the treatment of suspected severe allergic reactions following the administration of study medication (See Section 8.3. and Appendix 1). A trained physician, capable to handle severe, systemic allergic reactions, will remain on-site during the confinement period on all dosing visits. The subjects will be equipped with an indwelling venous cannula for 4 hours after dosing.

Blood samples for determination of tryptase will be taken in the event of a suspected Grade 3 or higher systemic allergic reaction. An initial sample should be taken approximately one hour after the onset of the reaction, with another sample taken at approximately three hours and then repeated every three hours until the Investigator is satisfied that the subject may be discharged. Blood sampling for tryptase must not delay initial resuscitation. Any subject that experiences a suspected Grade 3 or higher systemic allergic reaction must also have a blood sample collected for measurement of his/her baseline tryptase levels at the Follow-up visit.

Visit 2

During the first treatment visit (Visit 2), a single dose of 30 ng of DM-101 or corresponding placebo s.c. injection will be administered as described in Section 3.2. Table 12 (see Section 6.5) shows the procedures that will take place, before and after dosing. Dosing will be initiated only if the results of the pre-dosing brief medical review and other eligibility

assessments are satisfactory. The subjects will remain confined in Turku University Hospital's Emergency Care Unit for approximately 6 h following their dosing.

Treatment will be staggered in such a way that 2 sentinel subjects, 1 receiving DM-101 and 1 receiving placebo, will be dosed first in a double-blind fashion. Dosing of the remaining subjects in the cohort will be initiated no sooner than 22 h after the sentinel subjects have completed their Visit 2 dosing, without safety findings that would meet the study's stopping or treatment discontinuation criteria (see Section 9). Subjects in the main treatment group in each cohort will also receive treatment in a staggered way, with 2 subjects starting first to receive doses and the remaining subjects starting to receive doses no sooner than approximately 22 h after the first two subjects of the main group have completed their Visit 2 dosing.

Visit 2 of cohort 4 will not initiated until Visit 2 of cohort 3 has been completed.

All subjects will be given at the end of Visit 2, before discharge from the site, an adrenaline autoinjector and written instructions with an action plan on what to do if they develop a delayed allergic reaction (see Appendix 2).

Subjects will be contacted by telephone approximately 12 and 24 h after completion of dosing for a safety interview after each dosing visit.

Visits 3, 4, 5 and 6

After Visit 2, all subjects will return to the hospital on a biweekly basis for the subsequent dosings, to receive either a single s.c. injection or a series of 2 or 3 s.c. injections of the study medication. All dosings, except the 4th and 5th dosings of cohort 4, involve only single injections. In cohort 4, the administration of the study medication at Visits 5 and 6 involves 2 and 3 s.c. injections, respectively. There will be a minimum of 30 min interval between subsequent injections. Each injection will be given at a slightly different site of the exterior surface of the upper arm. The injections will alternate between the right and left arm.

On each of the Visits 3-6 dosing will be staggered in the same way as on Visit 2, ie. 2 sentinel subjects, 1 receiving DM-101 and 1 receiving placebo, will be dosed first in a double-blind fashion. Dosing of the remaining subjects in the cohort will be initiated no sooner than 22 h after the sentinel subjects have completed their dosing, without safety findings that would meet the study's stopping or treatment discontinuation criteria (see Section 9). Subjects in the main treatment group in each cohort will also receive treatment in a staggered way, with 2 subjects starting first to receive doses and the remaining subjects starting to receive doses no sooner than approximately 22 h after the first two subjects of the main group have received their dosing.

Visit 5 dosing of cohort 4 will only take place after a favorable recommendation from the SRC, once it has reviewed all available safety data so far collected in the study, including data from Visit 5 of cohort 3.

Dosing will only be allowed if the study's stopping and treatment discontinuation criteria have not been met.

Subjects will be contacted by telephone approximately 12 and 24 h after completion of dosing for a safety interview after each dosing visit.

Table 12 (for cohort 3) and Table 13 (for cohort 4) (see Section 6.5) show the procedures that will take place, before and after dosing, during the visits. All subjects will remain confined in Turku University Hospital's Emergency Unit for approximately 6 h following their dosing, and may then be discharged if the medical review by the Investigator or a designee is satisfactory.

6.4. Follow-up

All subjects will return to the clinical research unit 4 weeks (± 3 days) following the day of their last dose for a Follow-up visit (Visit 7).

Table 11 (see Section 6.5.) describes the procedures scheduled for the Follow-up visit for cohorts 3 and 4.

6.5. Schedule of Activity Tables for Study Visits

A general schedule of visits 2-7 activities is presented in Table 11. Tables 12 (for cohort 3) and 13 (for cohort 4) provide details of Visits 2-6.

Table 11. Cohorts 3 and 4 General schedule of activities (Protocol version 2.0)

Protocol Activity	Visit[1] Screening	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 Follow up
Days in relation to Visit 2	-60	0	14	28	42	56	84
Visit window, days	-60 - -7		±1	±2	±2	±2	±3
Informed consent	X						
Demographics	X						
IMP dosing		X	X	X	X	X	
General medical history	X						
Inclusion/Exclusion criteria	X						
Complete physical examination	X						X
Brief physical examination		X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X
Body temperature	X	X	X	X	X	X	X
Spirometry/FEV1[2]	X	X	X	X	X	X	X
ECG	X	X	X	X	X	X	X
Skin prick test	X						
Blood sample for specific IgE to Bet v components	X	X[4]	X[4]		X[4]		X
Blood sample for specific IgE to other than Birch common allergens	X						
Blood sample for safety lab tests	X	X	X	X	X	X	X
Blood sample for screening serology	X						
Urine dipstick test	X	X	X	X	X	X	X
Breath alcohol & urine drug screen	X	X	X	X	X	X	
Pregnancy test[3]	X	X	X	X	X	X	X
Serum FSH/ estradiol for postmenopausal women	X						
Blood sample for exploratory immunological biomarkers		X[4]	X[4]		X[4]		X
Blood sample for tryptase		X[5]					X[6]
Injection site examination[7]		X	X	X	X	X	X
Provision of adrenaline autoinjector and action plan in case of severe delayed allergic reaction		X					
Concomitant medication review	X	X	X	X	X	X	X
Adverse events		X[8]					
Phone calls		X	X	X	X	X	

[1]Screening can be split over 2 visits: Visit 1a is to confirm preliminary eligibility based on medical history and birch pollen allergy sensitivity (SPT) and Visit 1b to perform full screening assessments after initial eligibility has been confirmed.

[2]Spirometry assessments will be performed at screening. Measurement of FEV1 only will be performed at all other timepoints. Subjects with a history of asthma should not take short-acting beta agonists for a minimum of 4 h and long-acting beta agonists for 8 h prior to spirometry assessments.

[3]Pregnancy testing from serum for WOCBP should be performed at screening and be additionally arranged for 10 days prior to the dosing visit (Visit 2) according to the eligibility criteria, if the interval between the 2 visits is longer. Urine pregnancy test should be performed prior to dosing at Visit 2, Visit 3, Visit 4, Visit 5 and at Visit 6.

[4]Blood samples will be collected prior to the dose administration.

[5]Blood sample to be taken only in the event of a suspected Grade 3 or higher systemic allergic reaction, approximately 1 hour and 3 hours after the suspected reaction and then repeated every 3 hours until discharge.

[6]Blood sample for tryptase will be collected in any subject who has had a suspected anaphylactic response during the study treatment period (including subjects withdrawn from the study) to be used for baseline comparison.

[7]Injection site reactions will be captured as adverse events, as well as AE of special interest.

[8]Systemic allergic reactions will be captured as adverse events, as well as AE of special interest.

Table 12. Cohort 3 Visits 2-6. Detailed schedule of activities (Protocol version 2.0)

Protocol activity	Visit 2 / Visit 3 / Visit 4 / Visit 5 / Visit 6							
	Pre-dose	0	30 min	1 h	2 h	4 h	6 h	12 & 24 h
IMP dosing		X						
Brief physical examination	X						X	
Vital signs	X	X	X	X	X	X	X	
Body temperature	X			X		X	X	
FEV1	X			X		X	X	
ECG					X		X	
Blood sample for safety lab tests	X					X	X	
Urine dipstick test	X						X	
Pregnancy test (urine)	X							
Breath alcohol & urine drug screen	X							
Blood sample for specific IgE to Bet v components	X[1]							
Blood sample for explorative immunological biomarkers	X[1]							
Blood sample for tryptase		X[2]						
Injection site examination[3]		X	X	X	X	X	X	
Phone call								X[4]
Provision of adrenaline autoinjector and action plan in case of severe delayed allergic reaction							X	
Concomitant medication review	X							
Adverse events	X[5]							

[1] Pre-dose blood sample to be collected only on Visit 2, 3 and 5.
[2]Blood sample to be taken only in the event of a suspected Grade 3 or higher systemic allergic reaction, approximately 1 h and 3 h after the suspected reaction and then repeated every 3 h until discharge.
[3]Injection site reactions will be captured as AE, as well as AE of special interest.
[4]Subjects will be contacted by telephone 12 h and 24 h after dosing for a safety review.
[5]Systemic allergic reactions will be captured as AE, as well as AE of special interest.

Table 13. Cohort 4 Visits 2-6. Detailed schedule of activities (Protocol version 2.0)

Protocol activity	Visit 2 / Visit 3 / Visit 4 / Visit 5 / Visit 6								
	Pre-dose	0	30 min	1 h	90 min[8]	2 h	4 h	6 h[9]	12 & 24 h[9]
IMP dosing		X	X[1]	X[2]					
Brief physical examination	X							X	
Vital signs	X	X	X	X	X	X	X	X	
Body temperature	X			X			X	X	
FEV1	X			X			X	X	
ECG						X		X	
Blood sample for safety lab tests	X						X	X	
Urine dipstick test	X							X	
Pregnancy test (urine)	X								
Breath alcohol & urine drug screen	X								
Blood sample for specific IgE to Bet v components	X[3]								
Blood sample for explorative immunological biomarkers	X[3]								
Blood sample for tryptase		X[4]							
Injection site examination[5]		X	X	X	X	X	X	X	
Phone call									X[6]
Provision of adrenaline autoinjector and action plan in case of severe delayed allergic reaction								X	
Concomitant medication review	X								
Adverse events	X[7]								

[1]Dosing at 30 min time point only on Visit 5 and Visit 6.
[2]Dosing at 1 h time point only on Visit 6.
[3]Pre-dose blood sample to be collected only on Visit 2, 3 and 5.
[4]Blood sample to be taken only in the event of a suspected Grade 3 or higher systemic allergic reaction, approximately 1 h and 3 h after the suspected reaction and then repeated every 3 h until discharge.
[5]Injection site reactions will be captured as AE, as well as AE of special interest.
[6]Subjects will be contacted by telephone 12 h and 24 h after dosing for a safety review.
[7]Systemic allergic reactions will be captured as AE, as well as AE of special interest.
[8]90 min time point only on Visit 6 of Cohort 4.
[9]Calculated from the last injection

7. STUDY ASSESSMENTS AND PROCEDURES

This section describes each planned study assessment. The timing of each assessment is listed in Tables 11-13 in Section 6.5.

Whenever multiple assessments are scheduled to be performed at the same time, the clinical safety assessments should be made first.

7.1. Demographic and Baseline Information

The following demographic parameters will be recorded: date of birth, gender, race and ethnicity.

The subject's height (in centimeters) and body weight (in kilograms) will be measured.

A complete medical history, with an emphasis on allergy history, including history of allergic rhinoconjunctivitis and asthma, will be recorded at Screening. In addition, the medication (including over the counter and dietary supplements), alcohol, smoking and recreational drugs history, as well as information on previous participation in clinical trials and blood donation will be recorded and assessed, as related to the eligibility criteria listed in Section 4.2. With the subject's permission expressed in the ICF, the Investigator may ask for other information relevant for the subject's health and the purposes of the study from any health care provider who has possession of the subject's medical records.

7.2. Assessment of Safety

Planned time points for all safety assessments are listed in Tables 11-13 included in Section 6.5. Additional time points for safety tests, including vital signs, body temperature, ECG, spirometry, physical examination and laboratory safety tests may be added during the course of the study, if deemed necessary by the Investigator based on newly available data, to ensure appropriate safety monitoring.

7.2.1. Clinical Safety Assessments

Physical Examination

A complete physical examination will include assessments of the head, eyes, ears, throat, neck, skin, neurological, respiratory, cardiovascular, gastrointestinal, musculoskeletal system and lymph nodes.
A brief physical examination will include assessments of the skin, throat, respiratory, cardiovascular system and abdomen (palpation of the liver and spleen).

Vital Signs

Vital signs measurements will include systolic and diastolic blood pressure, pulse rate and respiratory rate. Vital signs will be recorded with the subject in a sitting or semi-recumbent position and after at least five min rest.

Two measurements will be taken at screening and prior to dosing. The mean value recorded prior to the first dosing of each day will be considered as baseline for that day.

Measurements that deviate substantially from previous readings will be repeated as soon as possible. All readings will be recorded in the subject's notes.

Body Temperature

Body temperature will be measured with an automated auricular thermometer.

Two measurements will be taken at screening and pre-treatment. The mean value recorded prior to the first treatment administration will be classed as baseline.

Readings that deviate substantially from the subject's baseline or are deemed not technically acceptable will be repeated as soon as possible. All readings will be recorded in the subject's notes.

Electrocardiogram

12-lead ECG will be recorded during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals and derives QTc(B).

Duplicate recordings will be obtained at Screening. The mean value recorded at Screening will be recorded as baseline. Single recordings will be obtained at the other determined timepoints during the study, except if according to the opinion of the Investigator there are abnormal findings and therefore triplicate ECGs should be obtained.

Spirometry

Standard spirometry will be performed at screening. Measurement of FEV1 will be performed at all other scheduled timepoints during the study. The clinical research unit will use their local standard procedures. Triplicate assessments will be made at screening and prior to the first dose on each dosing day. The best FEV1 (and the corresponding FVC at Screening) will be recorded in the eCRF. On the other time points, only single assessments will be made, unless the FEV1 result is below 90 % of that day's baseline result, in which case the FEV1 assessment will be repeated two more times. The best FEV1 will be recorded in the eCRF.

The best of three valid FEV1 readings recorded prior to the first dosing will be classed as baseline.

Subjects with history of asthma should not use short-acting beta agonists for 4 h or long-acting beta agonists for 8 h prior to the spirometry assessments.

Injection Site Examination

At each treatment visit, the injection sites will be examined immediately prior to and after treatment administration, as described in the Tables 11-13 in Section 6.5., for signs of reaction. Injection sites will also be examined during the Follow-up visit.

Reactions should be graded on a five-point (0 to 4) scale for each of the following parameters: pain, tenderness, erythema/redness, induration/swelling (see Table 14).

Table 14 Grading of Injection Site Reactions

Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalisation
Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalisation
Erythema / Redness[1]	None	2.5 to 5 cm	> 5 to 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration / Swelling[1]	None	2.5 to 5 cm and does not interfere with activity	> 5 to 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

[1]The parameter should be evaluated using the grading scale, as well as an actual measurement of the reaction at the greatest single diameter.

7.2.2. Laboratory Safety Assessments

Clinical Laboratory Assessments

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below. Reference ranges for all laboratory parameters will be provided by the local laboratory.

Haematology: Haematocrit, haemoglobin, red blood cells, white blood cells and differential WBC count (neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelets.

Biochemistry: Sodium, potassium, chloride, urea, creatinine, calcium, total protein, albumin, uric acid, total bilirubin, glucose, lactate dehydrogenase, creatine phosphokinase, alanine transaminase, aspartate transaminase, gamma glutamyltransferase, alkaline phosphatase, c-reactive protein.

Blood samples will be collected for assay of tryptase, in the case of a suspected severe allergic reaction (see Section 6.3.).

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Urine dipstick: pH, protein, ketones, leukocytes, blood and glucose; abnormal results will be followed up with particle counting and bacterial culture, as needed.

All laboratory tests with values that are clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or an adequate explanation is established.

Other Screening Tests

Pregnancy tests from serum and urine samples should be performed to all WOCBP, as described in the eligibility criteria (see Section 4.2) and indicated in Tables 11-13 in Section 6.5.

FSH and estradiol should be tested, as needed, at Screening in women of non-child bearing potential only (see eligibility criteria Section 4.2).

The subjects will also undergo screening serology tests for HIV (HIVAg/Ab), hepatitis B (HbsAg) and hepatitis C (HCVAb).

Alcohol breath test and drug urine screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) tests will be performed at Screening and at the start of each dosing day.

7.3. Assessment of Allergic Sensitisation

7.3.1. Skin Prick Testing

At Screening, SPT (performed on the flexor aspect of the forearm) with birch pollen allergen will be performed at the clinical research unit. Positive and negative controls will be included in the assessment (histamine and diluent, respectively).

Prior to the SPT, drugs that might interfere with this assessment (particularly oral antihistaminics and local skin application of glucocorticoids) must be avoided for 5 days.

The response to SPT will be assessed by measuring the orthogonal diameter of the wheal, at the mid-point of the longest axis, and the average of the longest and the orthogonal diameter will be calculated. Pseudopodia will not be assessed.

The mean wheal diameter of the negative control must be < 2 mm for the test to be considered valid. If the negative control wheal diameter is ≥ 2 mm, the test should be repeated on another day. The positive control should give a reaction with a wheal diameter ≥ 3 mm greater than the negative control.

7.3.2. Allergen-Specific IgE

A blood sample (10 ml) will be collected for the measurement of Bet v allergenic components (Bet v 1, Bet v 2, Bet v 4, Bet v 6)-specific IgE levels in serum by ImmunoCAP® at the Screening and other time points indicated in Tables 11-13 (see Section 6.5.).

In addition, the following allergen-specific IgE levels in serum will be measured at Screening only to allow better understanding of the allergic sensitization profile of the study participants:

- Alder, hazel, peanut, hazelnut, kiwi, celery, apple, peach, soy (cross-reactive allergens, Profilin 10 protein).
- Equine, cat, dog, mugwort, Timothy Grass, *Dermatophagoides pteronyssinus, Dermatophagoides farinae and Cladosporium herbarum*

7.4. Assessment of Efficacy

There are no efficacy assessments included in this study.

7.5. Assessment of Exploratory Immunological Biomarkers

Blood samples will be collected for potential analysis of immunological biomarkers that may be related to the effects of immunotherapy, including birch pollen-specific immunoglobulins (IgG sub-classes and IgA), blocking antibodies, B and T cell phenotyping, and cytokines. The samples will be analysed in a qualified laboratory. After completion of the analyses the remaining blood will be destroyed, unless the subject has given separate, optional consent for their further storage for additional potential biomarker analyses related to the purposes of the study.

7.6. Assessment of Pharmacokinetics

There are no pharmacokinetic assessments included in this study.

7.7. Optional Sub-study: Assessments

A separate optional sub-study may involve collection of medical history information and a blood sample collection for analysis of exploratory immunological biomarkers after the 2021 birch pollen allergy season, i.e. in the autumn of 2021. Only participants in cohorts 2 - 4 will be invited to take part in this sub-study. This sub-study does not involve any other assessments or procedures except an interview and the blood sample collection. Separate consent will be asked for participation in this optional sub-study.

8. ADVERSE EVENTS

The Investigator and his staff are responsible for detecting, documenting and reporting events that meet the definition of an AE. Adverse events will be reported, irrespective of whether they are volunteered, elicited, or noted on physical examination or medical review, throughout the study, from the signing of the ICF until the Follow-up visit.

AEs occurring prior to the first treatment administration, but after obtaining informed consent will be reported separately from TEAEs, which will be of particular interest.

Definitions of AEs and serious adverse events (SAE) and the documentation and reporting of them within this study will follow the GCP, EU and Finnish national guidance.

8.1. Definition of Adverse Events

An AE is any untoward medical occurrence experienced by a study subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. For the current study, all AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 22.1) by 4Pharma in co-operation with CRST.

An AE can therefore be any unfavorable and unintended signs (including clinically relevant changes in laboratory parameters), symptoms, diseases (new or exacerbated) or accidents temporally associated with the use of a medicinal product.

AEs comprise all disturbances of general health status. Events meeting the definition of an AE include:

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, spirometry, vital signs measurements), including those that worsen from baseline, and the Investigator considers them clinically significant.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction with the study treatment.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events that do not meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.2. Definition of Serious Adverse Events

A SAE is any AE occurring during the study that results in any of the following outcomes:

- Results in death
- Is life-threatening. The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization. This is defined as the subject being hospitalised overnight. Any pre-planned or anticipated in-hospital visits must be documented in advance at the screening visit and will be excluded from this category.
- Results in significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event that may require medical or surgical intervention to prevent one of the above outcomes.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject and may require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered to be SAEs.

8.3. Definition of Suspected Unexpected Serious Adverse Reactions

An unexpected adverse drug reaction is any adverse drug reaction (ADR), the specificity or severity of which is not consistent with the current IB of DM-101. In this FiH study, all adverse reactions to DM-101 will be considered unexpected. Suspected unexpected serious ADRs (SUSARs) are subject to expedited reporting to the CA by the pharmacovigilance provider (PV) of the study. The investigator reports all authority-reportable AEs to the Sponsor and the

pharmacovigilance provider, for reporting to the CA according to applicable legislation, and as agreed between the parties

8.4. Definition of Adverse Events of Special Interest

8.4.1. Systemic Allergic Reactions

All allergic reactions that occur after the initiation of IMP dosing should be recorded in the subject's medical records and also as an AE in the eCRF. If a systemic allergic reaction meets the definition of serious, then it should be classified as a SAE and will be recorded and reported in the same way as any other SAE.

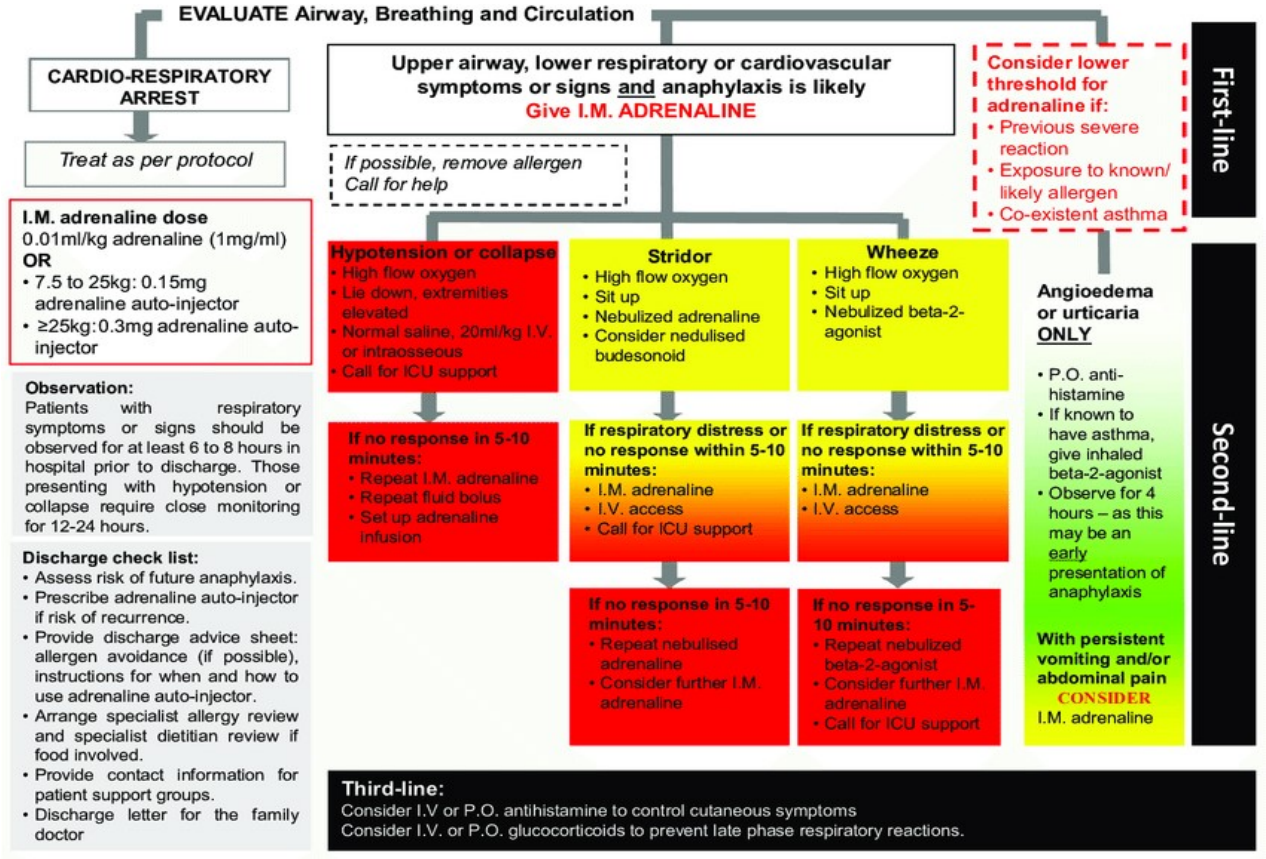
In addition, all systemic allergic reactions must be graded, as defined by the WAO Subcutaneous Immunotherapy Systemic Reaction Grading System (Appendix 1) and be considered AEs of Special Interest (AESI). All Grade 2 to 5 systemic allergic reactions must be reported in an expedited manner to the Sponsor within 24 h from their occurrence.

Treatment of systemic allergic reactions

Systemic allergic reactions may be life-threatening and any suspected severe allergic reaction must be treated immediately.

All medications and medical equipment for the treatment of suspected, severe allergic (anaphylactic) reactions must be immediately available at the clinical research unit.

Figure 2 presents an example of an algorithm for the management of suspected anaphylactic reactions, proposed by the European Academy of Allergy and Clinical Immunology (EAACI).The Investigator will follow CRST's Standard Operating Procedure (SOP) for treating suspected anaphylactic reactions, and a copy of the Guideline and the SOP must be placed in the ISF. The subjects of cohorts 3 and 4 will be equipped with i.v. cannula until at least 4 h after the last injection of the day, and the i.v. route will therefore be available for fluid therapy and for administration of antihistaminics and glucocorticoids.



From Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology Muraro A et al., 2014 Allergy. 69:1026-1045.

Figure 2 Schematic illustration of the initial management of anaphylaxis proposed by the EAACI.

If a delayed, systemic allergic reaction occurs following dosing, once a subject has left the clinical research unit, the subject should follow the action plan provided to him/her by the Investigator at Visit 2 (See Appendix 2). Subjects should also contact their health care provider or seek emergency medical attention, as indicated.

Subjects who develop Grade 3 and 4 systemic allergic reactions should be hospitalised overnight or monitored for at least 12 hours.

8.4.2. Injection Site Reactions

All allergic reactions that occur after the initiation of IMP dosing should be recorded in the subject's medical records and also as AESI in the eCRF.

All Injection site reactions should be evaluated as AEs and also be graded on a five-point (0 to 4) scale for each of the following parameters: pain, tenderness, erythema/redness, induration/swelling (Table 14).

8.5. Recording of Adverse Events

When an AE or SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The Investigator will then record all relevant information regarding the event in the subject's medical record and transcribe it to the eCRF.

When recording an AE / SAE, the following details must be given:

- Event observed (brief description using medical terminology)
- Start and stop dates and times
- Severity (Section 8.5.1.)
- Causality (Section 8.5.2.)
- Relationship to other events (e.g. study procedure or concomitant medication)
- Action taken (brief description)
- Outcome
- Serious (Yes/No)

When an AE occurs, the Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

All AEs will be recorded as they are reported, whether spontaneously volunteered by a subject or in response to questioning about well-being at each study visit. The subject will be questioned in a general way and no specific symptoms will be suggested. The questioning about AEs will cover the current visit and the period of time between the previous and current visit although subjects may report AEs occurring at any other time during the study. Follow-up of all AEs will continue until the overall clinical outcome is definitive.

8.6. Evaluation of Adverse Events and Serious Adverse Events

8.6.1. Assessment of Intensity

The Investigator will assess the intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

Mild	An event that is noticeable, but easily tolerated by the subject, causing minimal discomfort and not interfering with usual daily activities, compared to subject's baseline.
Moderate	An event that is sufficiently discomforting to interfere with usual daily activities, compared to subject's baseline.
Severe	An event that prevents usual daily activities, compared to subject's baseline.

8.6.2. Assessment of Causality

When an AE or SAE occurs, the Investigator should assess the relationship between the IMP and the occurrence of the event. The Investigator should use clinical judgment to determine the relationship and assign it to one of the following categories:

Related	Any event that has a reasonable temporal relationship with the administration of study medication or follows a response pattern known to be related with the study IMP.
Unlikely to be related	Any event that does not have a reasonable temporal relationship with the administration of study medication and does not follow a response pattern known to be related to the study IMP.
Not related	Any event that started before administration of study medication and/or for which there is a clear alternative explanation.

The same criteria will be used to assign causality to study procedures.

8.7. Follow-up of Adverse Events / Serious Adverse Events

After the initial AE or SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. New or updated information will be recorded in the originally completed data collection tool.

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations that may be indicated, including (but not limited to) additional laboratory tests, histopathology or consultation with other health care professionals. If a subject dies during participation in the study or during a recognized follow-up period, the Investigator should provide a copy of any post-mortem findings, including histopathology.

8.8. Reporting of Adverse Events and Serious Adverse Events

Once the Investigator determines that an event meets the definition of a SAE, the SAE should be reported to the pharmacovigilance provider (PV) and Sponsor within 24 h, regardless of the time that may have elapsed since the time the event occurred and regardless of the causal relationship of IMP to the event. Any follow-up information on a previously reported SAE should also be reported to the PV and Sponsor later as needed. SAEs should be followed up until resolved or until the event is considered chronic and/or stable outcome.

The PV provider in this study is A+ Science. Contact details and instructions for SAE reporting to PV provider and Sponsor's Medical Monitor will be located in the ISF. The PV provider reports all authority reportable AEs to the CA.

8.9. Reporting of Pregnancy

Subjects who become pregnant during the treatment period must receive no further study treatment and the pregnancy must be reported using the same procedure as for SAE (Section 8.7). Subjects who become pregnant once treatment administration has been completed may remain in the study and the pregnancy must be reported using the same procedure as for SAE. A Pregnancy Notification Form must be completed. The outcome of the pregnancy should be followed up until term or premature termination. A Pregnancy Outcome Form, to assess the health of the mother and any infants, should be completed and reported following the same procedure as the Notification Form.

9. PREMATURE STUDY AND TREATMENT STOPPING CRITERIA FOR COHORTS 3 AND 4

The progress of the study will be monitored by the SRC (see Section 3.3.) The committee will review all safety data at timepoints defined in the study design (see Section 3) and will make recommendations regarding continuation, suspension or modification of dosing.

9.1. Study Stopping Criteria

The Sponsor reserves the right to prematurely terminate the study for valid scientific or administrative reasons.
For reasons of safety, further dosing in the study will be suspended and all safety data will be reviewed by the SRC if any of the following happens:

- Death of a study participant possibly attributable to study treatment or procedure.
- One Grade 4 systemic allergic reaction according to the WAO classification, following injection of the study IMP.
- Two Grade 3 systemic allergic reactions according to the WAO classification, following injection of the study IMP in 2 participants in the same cohort.
- One Grade 4 injection site reaction in 3 participants in the same cohort.

If a decision to suspend dosing in the study is reached, the SRC will review thoroughly all safety data and will determine whether:

- Dosing (scheduled or adjusted) may be re-started in current or subsequent cohorts.

- The study must be stopped and no additional subjects be dosed.

The EC and the CA will be informed, if the study is terminated prematurely. The Investigator will proceed to appropriate actions concerning the study subjects in the case of premature termination of the study.

9.2. Treatment Stopping Criteria

For an individual subject, dosing of study IMP will be discontinued if any of the following happens:

- One Grade 4 systemic allergic reaction according to the WAO classification, following injection of the study IMP.
- Two or more Grade 3 systemic allergic reactions according to the WAO classification, following injection of the study IMP.
- One Grade 4 injection site reaction.
- Two Grade 3 injection site reactions following two injections.
- An AE or need for medication not consistent with the protocol requirements that, in the judgment of the Investigator, presents an unacceptable consequence or risk to the subject.
- Inability or unwillingness to comply with the study protocol or protocol deviation that is considered sufficient to jeopardize the subject's well-being or the integrity of the study.
- Pregnancy during study participation.
- Withdrawal of consent

Discontinuation of dosing will not necessarily result in withdrawal of the subject from the study. For the subjects who discontinue treatment, all safety assessments scheduled for the Follow-up will be requested and observations will be recorded.

9.3. Dose Adjustment Criteria

For each individual subject, dose escalation will be halted and dosing will be adjusted according to the following:

- If a Grade 3 systemic allergic reaction, according to the WAO classification, or a Grade 3 injection site reaction occurs, following administration of a dose of the study IMP, the previous well-tolerated daily dose level should be repeated at the time the next dosing is scheduled. If this is found to be tolerated, the subject will continue to receive the same, tolerated dose level at each subsequent scheduled dosing. Further dose escalation according to the protocol's pre-defined scheme should not be attempted. The number of doses scheduled for one dosing day should not be exceeded.

10. STATISTICS AND DATA MANAGEMENT

10.1. Estimation of Sample Size

A total of 27 subjects will be randomized into the study; additional subjects may be included to replace discontinued subjects in cohorts 3 and 4. Cohort 1 included 6 subjects, and 5 of the planned 8 subjects were included in cohort 2 before the study was temporarily halted. No new subjects will be included in cohort 2 after re-start of the study (Protocol version 2.0). Cohorts 3 and 4 will include 8 subjects each. The selected sample size is not based on any formal power calculations.

10.2. Statistical Methods

A summary of the statistical methods is given below.

10.3. Statistical Analysis Plan

Detailed statistical analysis information will be provided in a separate Statistical Analysis Plan (SAP) before the database lock.

10.4. Statistical Hypotheses

No formal statistical hypotheses are stated in this study. The primary objective of the study is the evaluation of safety and tolerability of s.c. administration of DM-101 in adult subjects with birch pollen allergy. Safety and tolerability data will be analysed descriptively.

10.5. Data sets to Be Analysed

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.

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

10.6. 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 and by cohort. In case inferential statistical analyses are conducted, a 2-sided p-value of less than 0.05 is considered statistically significant.

10.7. Demographic and Baseline Characteristics

The demographic and baseline characteristics of the subjects will be presented using descriptive summary statistics by cohort and treatment.

10.8. Analysis of Efficacy Variables

Not applicable.

10.9. Analysis of Safety Variables

The primary endpoint of the study is the number of all 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. Also, separate tabulations by treatment will be provided. For each preferred term, the average number of events will be calculated. In addition, TEAEs will be reported by causality and severity.

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.

Local injection site reactions (pain, tenderness, erythema/redness, induration/swelling) will be graded on a five-point (0 to 4) scale. These will be presented and summarized by cohort and treatment.

Other safety variables include results from physical examination, vital signs, clinical laboratory values and spirometry. The results will be presented using descriptive statistics by cohort and treatment.

10.10. 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.

10.11. Analysis of Exploratory Variables

Descriptive statistics and visualizations will be provided for immunological biomarkers. Also exploratory statistical analyses will be conducted to provide preliminary information on the used doses as compared to placebo, if feasible. Details of these analyses will be given in the statistical analysis plan (SAP).

10.12. Data Management

Technical and detailed elaboration of the principal features of data management (DM) will be available in a separate Data Management Plan (DMP) specifically written for this study.

10.13. Database Design

The study database and data entry screen design, as well as edit checks will be defined according to the corresponding eCRFs and the study protocol.

10.14. Data Entry

Data will be collected on eCRFs designed in accordance with the study protocol. The investigator or designated study site personnel will enter subject data into the eCRFs as soon as possible during or after the subject's visit. All data entries in the eCRFs should be consistent with the source documents. The investigator will electronically sign the data to confirm that all the information is accurate and correct.

10.15. The Query Process

The Study Monitor will review the eCRFs and compare them with the relevant source documents to ensure the validity and accuracy of the study data. If corrections are needed, the Study Monitor will raise a query in the eCRF. The investigator or designated study site personnel will answer the queries and make the needed corrections or alterations.

10.16. Medical Encoding

AEs and medical history verbatim terms will be coded using MedDRA version 22.1. Concomitant Medications verbatim terms will be encoded using the Anatomical Therapeutic Chemical (ATC) classification system (ATC Index, WHO Collaborating Centre for Drug Statistics Methodology), most recent version held by 4Pharma.

10.17. Database Lock

When all data have been entered and discrepancies have been solved, the database can be locked. The locked database is used in the final statistical analyses for study reporting.

10.18. Software

Viedoc™ Clinic version 4.50 or newer will be used as an EDC system in this study. SAS® for Windows version 9.4 or newer will be used in randomization, statistical analysis and reporting of the study data.

11. STUDY MANAGEMENT

11.1. Study Monitoring

The study will be monitored by a qualified Clinical Study Monitor appointed by Crown and approved by the Sponsor. The study monitor will not be otherwise involved in study conduct and will be allowed to monitor the study as frequently as necessary to ensure that data recording and protocol adherence are satisfactory. The eCRFs and related source data will be reviewed in detail and 100 % source data verification will be performed. A Clinical Study Monitoring Plan will be prepared by Crown and approved by the Sponsor before the study start.

11.2. Quality Control and Quality Assurance

During the clinical execution of the trial, the SOPs of CRST are followed, unless otherwise agreed between the parties. For DM and statistics, the SOPs of 4Pharma are followed. For study monitoring, the SOPs of Crown are followed. The principles of GCP are followed throughout the study. The analyses of hematology and clinical chemistry will be performed at TYKSLAB, the accredited clinical laboratory of Turku University Hospital. The analyses of serum levels of allergen specific IgE will be performed at Yhtyneet-Medix Laboratoriot Oy. Laboratory quality certificates will be available.

The quality assurance personnel of Crown and the Sponsor may conduct audits in any phase of the study. The study may also be inspected by CAs.

A curriculum vitae in English will be obtained from all investigators who sign the protocol and from other relevant persons.

11.3. Deviations

Non-subject specific protocol deviations will be documented in Deviation Log maintained by the study monitor. Deviations concerning a single subject will be described in the corresponding eCRF. Protocol deviations will be classified as major or minor by the Sponsor.

11.4. Amendments

Minor changes (e.g., concerning logistics or administration) to the clinical study protocol can be clarified in a NtF or in a non-substantial amendment, if the change has no effect on the safety of the subjects or on the scientific value of the study. The investigator will inform the Sponsor of such minor changes. All essential changes to the clinical study protocol are described in a substantial amendment, which is submitted for approval by the EC and CA before adopting the changes, except when necessary to eliminate immediate hazards to the study subjects. Amendments to the clinical study protocol are prepared as agreed by the parties involved in the study.

12. REGULATORY AND ETHICAL CONSIDERATIONS

This study will follow the relevant regulations and guidance for biomedical research involving human subjects, such as the Declaration of Helsinki, ICH GCP, and national and EU legislation. Special emphasis will be put on the well-being of the subjects.

Prior to initiation of the study, the study protocol, the subject information leaflet and the ICF and the texts of any advertisements used for the recruitment of study subjects will be submitted to and approved by an independent EC. The EC will also be notified of any other materials to be given to the subjects (e.g. study subject diary, participation card). The study will be authorized by the CA (the Finnish Medicines Agency, Fimea) before its commencement.

The study subject candidates will be provided with both verbal and written information on the study, its risks and benefits. They are encouraged to ask questions on the study. After having had enough time to consider their participation, they may sign the ICF. No study procedure will be implemented prior to obtaining written IC that is signed by the subject at the time of consent. A copy of the signed ICF will be given to the subject. The investigator will keep each subject's signed ICF on file for inspection by a regulatory authority at any time.

The subjects are told what personal information will be collected of them and how. The collection of personal information is described in compliance with the EU General Data Protection Regulation; the description is kept in the ISF and is made available to the subjects, if they wish. The investigator assures that the privacy of the subjects, including their personal identity and all medical information, will be maintained at all times.

No personal medical benefits can be expected from participating in the study. The participation will be compensated and the amount of payment will be approved by the EC.

For an ethical evaluation of this trial with no direct benefits to the participants, a risk analysis has been carried out. This FIH trial is to be performed in otherwise healthy subjects who are allergic to birch pollen. The aim is to investigate the safety and tolerability of a novel, recombinant, modified birch pollen allergen (DM-101), in order to allow further clinical development of DM-101 as a novel treatment for birch pollen allergy. The main risk identified in this analysis is that of an allergic reaction evoked by exposure to DM-101. Based on available nonclinical evidence, DM-101 should be less prone to evoke acute allergic reactions compared to other products currently used in s.c. AIT of birch pollen allergy, but this cannot be considered certain at this stage as relevant evidence in humans is lacking, since this is the first clinical trial with DM-101. Specifically, the following precautions and risk mitigation measures have been employed in the planning of this study in order to minimize the risks to study participants:

- Subject selection criteria are such that unnecessary risks are avoided; subjects should be in good health, not having concomitant illnesses or using medications that might interfere with subject safety or study assessments;
- Sentinel dosing and staggered dosing will be employed;
- The starting single dose and the dose escalation protocol for repeated administration have been selected based on all available evidence, including observations made in cohort 1 and 2 subjects of this study;

- Rescue medication (adrenaline, i.v. and oral antihistaminics, i.v. and oral glucocorticoids) will be available, there will be written procedures in place for their use, and subjects should not have contraindications to their use; venous cannulae will be in place on the dosing visits; adrenaline autoinjectors and written instructions on what to do in case of a late allergic reaction will be provided upon discharge on the first dosing visit; in case of late-appearing reactions, a study physician will be available 24/7 by phone.
- Subjects of cohorts 3 and 4 will remain confined at Turku University Hospital until 6 h after dosing.
- The trial will be carried out outside of the birch pollen season in Finland, to avoid co-exposure to the natural birch allergen.
- Progression to subsequent dosing cohorts will take place only if the PI's and SRC's review of the collected safety and tolerability data from each preceding cohort is favorable; dose escalation within each cohort will also take place only if safety allows it and the study's dosing discontinuation or adjustment criteria have not been met.

Other possible risks and the measures taken for their mitigation are the following:

- Induction of birch pollen allergy by exposure to DM-101: subjects will be selected based on documented evidence of allergy to the major birch pollen allergen Bet 1 v; thus, exposure to DM-101 should not evoke allergy in a subject not previously sensitized.
- Unexpected findings in any of the evaluations carried out for the purposes of the study: any such incidental findings will be adequately communicated to the subject in question, with appropriate counseling on the need for medical care or follow-up;
- Unexpected AEs related to DM-101, other than allergic in nature: unexpected mechanisms for causation of AEs are always possible in early-phase clinical trials, but their likelihood is small as the employed doses of DM-101 are small (at most, 710 ng), and as repeated dosing of 0.5 mg doses was well tolerated in the GLP toxicity study performed in rabbits. The team will monitor the subjects closely for any unexpected AEs and appropriate measures will be taken, if needed, for their treatment. The measures taken for mitigation of allergy risks are also applicable to other possible AEs.

The subjects will be followed closely for possible AEs and specific dosing interruption criteria are included in the study protocol to ensure subject safety. A SRC will also monitor subject safety and will make recommendations on further dosing and possible modifications to the study.

An invasive procedure included in this study is venous cannulation on the dosing visits. Venous cannulation may result in feelings of discomfort and pain, haematoma, thrombophlebitis and vasovagal reactions, but it is considered warranted for subject safety, facilitating administration of fluids and rescue medication (antihistaminics and glucocorticoids) in case of an anaphylactic reaction or other emergency. Apart from dosing, venous cannulation and venipuncture for collection of blood samples, all other study procedures are considered non-invasive. The volume of blood drawn from each subject will not exceed 200 ml in cohort 1 and 450 ml in cohorts 2-4. This blood loss should not produce any adverse effects.

The subjects are urged to report all AEs to the study personnel and they are given phone numbers of the investigator, the study nurses and CRST's 24/7 on-call physician whom they are instructed to contact if they observe potentially significant AEs, or in other urgent study-related issues.

Substantial changes to the final approved protocol will be initiated only with the EC's favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the study subjects. When a change involves only logistics or administration, it will be considered non-substantial, and needs not be submitted to the EC or the CA for approval. The CA will also be notified before adopting a substantial amendment.

The trial has been registered in a publicly accessible database prior to study start. After the study has been completed and a Clinical Study Report prepared, the EC and CA will be notified of the study results, and a summary of the results will be posted in a publicly accessible database. The study results are also intended to be published in a peer-reviewed scientific journal, with authorship criteria and other publication-related issues in agreement with established ICMJE guidance.

13. DATA HANDLING AND RECORD KEEPING

13.1. Case Report Forms

Generated subject data will be recorded on eCRFs provided for this study by 4Pharma. Only authorized persons, as agreed at the study initiation meeting, are allowed to make entries on eCRFs. Agreed study team members can make corrective entries on the eCRFs if the Investigator has not yet signed the eCRF page. After signing, only the Investigator is allowed to make corrections.

eCRFs are required for each study subject. They will be completed in English by the Investigator or other authorized study personnel. The Investigator has to confirm the content of the eCRF by an electronic signature.

Corrections to the eCRFs can be made by the Investigator or other authorized study personnel. An audit trail within the system will track all changes/corrections made.

Instructions and training for completing the eCRFs will be provided. These instructions will cover the content and technical issues of the EDC system.

13.2. Source Data

Study-specific source data forms will be prepared by CRST's study personnel or provided by the Sponsor before study initiation. Access to the source data revealing the identity of the study subjects is only to study personnel. The generated source data are stored at CRST.

The results of the laboratory blood and urine safety determinations are stored as print-outs within the ISF at CRST and in the patient records of TYKSLAB, Hospital District of Southwest Finland, the personnel of which is bound to professional secrecy. The coded 12-lead ECG and spirometry print-outs are stored at CRST.

The contact information of the subject's next-of-kin will be destroyed before the ISF is archived.

14. STUDY SCHEDULE

The clinical study is planned to be performed during Q3/2019-Q2/2021.

15. FINANCING AND INSURANCE

Financial matters are covered by an agreement between CRST and the Sponsor, and in respective agreements with the other relevant parties of the study. The Sponsor has an insurance policy (Lääkevahinkovakuutus) covering damages caused by the investigational products administered during the study. The insurance statement will be provided in the ISF and TMF (Trial Master File). In case of any injury caused by an incident that is related to the study procedures but is not causally related to the investigational products, study subjects will be covered by the patient insurance of CRST.

16. STUDY REPORT AND PUBLICATION POLICY

A final study report will be prepared in accordance with relevant ICH guidance, as agreed between the parties, after the study has been completed or prematurely terminated. The Sponsor may submit the report to another party. The EC and CA will be notified about the study completion according to laws and regulations and as agreed between the parties. The study report will be approved by the Investigator and the Sponsor. The Sponsor remains the exclusive owner of the study data defined in the protocol. The eventual publication of the study results and the authorships of the eventual publications will be mutually agreed later. The planned publication will not be submitted for publication without prior approval of the Sponsor.

17. ARCHIVING

The ISF (including e.g. source data, subject screening and identification logs, original signed ICFs, copies of CRFs, and drug accountability records) will be archived by CRST to enable possible follow-up assessments or audits by the Sponsor, or inspections by regulatory authorities. The ISF is archived for at least 15 years after the end of the study, unless specified otherwise by a written agreement between the Sponsor and CRST.

Information collected during the course of this study will be stored by the Sponsor and used in the development of DM-101 in its development as a treatment for birch pollen allergy, and thereafter for as long as the information is relevant to patient care. Its use includes the transfer of data to regulatory authorities of the EU or its member states, the USA or other countries for the purpose of obtaining, maintaining and processing of marketing authorizations. All information is handled confidentially and according to the current laws and regulations.

The Sponsor will archive the TMF according to current laws and regulations.

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