CLINICAL STUDY REPORT SYNOPSIS

Study Title	A multicentre, open label, phase IIb clinical trial to evaluate safety, tolerability and efficacy of the depigmented modified allergen extract of two mites mixes at 200 DPP/ml (DP/MG/14-2 *Dermatophagoides pteronyssinus / Lepidoglyphus destructor* and DP/MG/14-1 *Dermatophagoides pteronyssinus /Blomia tropicalis*) in subjects with allergic rhinitis or rhinoconjunctivitis, with controlled allergic asthma.
Study Code	1301-PG-PSC-203
Test Products	DP/MG/14-1 and DP/MG/14-2
Phase	IIb
Sponsor	LETI Pharma S.L.U. (current name of the company since January 2021, previously named Laboratoris LETI S.L.U.)
Coordinating Investigator	Dra. Carmen Vidal Complejo Hospitalario Universitario de Santiago

Study Initiation Date	22/09/2014	**Study Completion Date**	09/05/2018

Report Version	1.0	**Report Date**	31/05/2021

Compliance Statement

This study was conducted in compliance with the International Council for Harmonisation (ICH) Good Clinical Practices (GCP), including the archiving of essential documents.

Title	A multicentre, open label, phase IIb clinical trial to evaluate safety, tolerability and efficacy of the depigmented modified allergen extract of two mites mixes at 200 DPP/ml (DP/MG/14-2 *Dermatophagoides pteronyssinus / Lepidoglyphus destructor* and DP/MG/14-1 *Dermatophagoides pteronyssinus /Blomia tropicalis*) in subjects with allergic rhinitis or rhinoconjunctivitis, with controlled allergic asthma.		
Study Code	1301-PG-PSC-203	**EudraCT**	2014-000172-26
Sponsor	LETI Pharma, S.L.U. C/Sol 5 28760 Tres Cantos, Madrid, España		
Investigational Medicinal Products (IMPs)	DP/MG/14-1 *D. pteronyssinus / B. tropicalis* and DP/MG/14-2 *D. pteronyssinus / L. destructor*		
Coordinating Investigator	Dra. Carmen Vidal Complejo Hospitalario Universitario de Santiago Servicio de Alergología Travesía de Choupana, s/n, 15706 Santiago de Compostela		
Study Period	Initiation date (FPFV): 22/09/2014 Study completion date (LPLV): 09/05/2018 Data Lock Date: 30/04/2019		
Phase of Development	IIb		
Background and Rationale for the Study	House dust mites play an important aetiological role in patients with allergic respiratory diseases, such as allergic rhinitis and allergic asthma, in geographic regions with considerable exposure. Worldwide, *D. pteronyssinus* is the dominant species among house dust mites, but with huge differences between different geographical regions. Moreover, storage mites may also be significant in some geographic regions. Finally, it is noteworthy that a relevant percentage of patients are sensitised to more than one species of dust mite. The most prevalent dust mites causing allergy-related diseases in Spain are *D. pteronyssinus*, *D. farinae*, *L. destructor* and *B. tropicalis. B. tropicalis* is a clinically relevant species in tropical and subtropical regions, coexisting with *D. pteronyssinus,* and dual sensitisation to both is quite common. In Spain, *B. tropicalis* allergens are considerable in the Canary Islands. In addition, *L. destructor* can often be found in half of all homes in Northern Spain, and approximately 60% of patients in these regions are simultaneously sensitized to *L. destructor* and to *D. pteronyssinus.* *L. destructor* and *B. tropicalis* do not present known allergens in common with dust mites from the genus *Dermatophagoides*, suggesting that double		

	sensitisation is responsible for the respiratory symptoms that occur in sensitised allergic patients and that, when immunotherapy with allergens is indicated, both species must be represented in treatment at the same time. It is widely documented that sensitised allergic patients must be exposed to variable concentrations of allergen sources to present allergy symptoms. The concentration required to start an allergic response varies significantly from one person to another, depending on immune factors, allergen exposure, climactic conditions, period of exposure, individual sensitisation, etc. Not all people need to be exposed to the same quantity of allergen to develop an allergic reaction; this is mainly due to the fact that the threshold for presenting allergic symptoms varies from one population to another. It has also been shown that the efficacy of immunotherapy is dose-dependent. Products are currently manufactured based on biological potency according to EMA guidelines, but taking into consideration the main allergen content. Considering the previously revealed need to have vaccines with complete-dose mite mixtures for patients sensitised to both species, the safety and tolerability of the two most commonly presented mite combinations will be researched in this clinical study: • DP/MG/14-1 D *pteronyssinus*/*B. tropicalis* and DP/MG/14-2 *D. pteronyssinus*/*L. destructor* are indicated for the treatment of type I (IgE-mediated) immediate allergic diseases such as allergic rhinitis, allergic conjunctivitis and/or allergic rhinoconjunctivitis, with or without controlled asthma, caused by allergic substances in *D. pteronyssinus* and *B. tropicalis* or *D. pteronyssinus* and *L. destructor*. • DP/MG/14-1 *D. pteronyssinus*/*B. tropicalis* and DP/MG/14-2 *D. pteronyssinus*/*L. destructor* belong to the drug class of allergen extracts. In both cases they contain depigmented, polymerised allergen extracts of a mixture of *D. pteronyssinus* and *L. destructor* or *D. pteronyssinus* and *B. tropicalis* adsorbed on aluminium hydroxide gel. Other ingredients in the compound include: sodium chloride, phenol and water for injection. They are developed in the form of a solution for injection for specific immunotherapy (hyposensitisation). These two mite mixture products would thus cover the main geographic regions influenced differently by storage and house dust mites in Spain.
Objectives	**Primary Objective** To evaluate the safety and tolerability of two allergens extract of mites mixtures (DP/MG/14-1 *D. pteronyssinus / B. tropicalis* at and DP/MG/14-2 *D. pteronyssinus / L. destructor*) administered, using a *rush* build-up phase in subjects with allergic rhinitis or rhinoconjunctivitis, with controlled asthma. **Secondary Objectives** To evaluate the efficacy by means of the Combined Symptom and Rescue Medication score (cSMS) on nasal, ocular and pulmonary symptoms and their respective Rescue Medication score for the perennial treatment regimen of allergen extract of two mites mixes (DP/MG/14-1 and DP/MG/14-2) after 2 years of treatment compared with baseline. Other efficacy parameters will be evaluated: changes in Asthma Control Questionnaire (ACQ), Visual Analogue

	Scale (VAS) and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) / Asthma Quality of Life Questionnaire (AQLQ). **Exploratory Objectives** To evaluate the mechanism of action of the treatment with DP/MG/14-1 and DP/MG/14-2, administered subcutaneously by measuring immunology laboratory parameters such as specific-IgE and IgG4 of DP/MG/14-1 and DP/MG/14-2 completed allergen extract mites.
Methodology	Prospective, non-randomized, non-controlled and open safety study. This was an open-label, non-controlled, non-randomized, prospective safety study in subjects with rhinitis or allergic rhinoconjunctivitis, with controlled asthma, and clinically relevant sensitization to dust mites from the *Pyroglyphidae* and *Glycyphagidae* families. Subjects received specific subcutaneous immunotherapy for said allergens with a dust mite mixture of DP/MG/14-1 and DP/MG/14-2 at several sites in Spain. The suitable IMP composition was used according to each subject's sensitization profile, whether: • DP/MG/14-1 *D. pteronyssinus / B. tropicalis* (100/1000 DPP/ml or 100/500 DPP/ml) or: • DP/MG/14-2 *D. pteronyssinus / L. destructor* (100/100 DPP/ml) Administration of the IMP was performed in two phases: • Rush build-up phase: on the first day of administration, IMP was administer in the form of two subcutaneous injections of 0.2 ml and 0.3 ml with a 30-minute interval between the two administrations. • Maintenance phase: on the second day of administration, 0.5 ml were administered, and the following 23 months subjects received a monthly dose of 0.5 ml, according to routine clinical practice. Eight visits were scheduled: screening visit (Visit 1), first rapid scaled dose administration (Visit 2), first maintenance administration one month later (Visit 3), final follow-up safety visit one week later (Visit 4), four efficacy follow-up visits at 6, 12, 18 and 24 months (Visits 5, 6, 7 and 8). At all study visits the following parameters were assessed: • ACQ, RQLQ and AQLQ questionnaires. • VAS • Symptom and medication subject diary filled by the subjects daily 15 days before each study visit Blood samples were collected at screening visit (Visit 1) and at the end-of-study visit (Visit 8) to assess safety parameters (Hematology, including RBCs, hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelets and leukocytes, and biochemistry, including glucose, creatinine, ALT/SGPT, AST/SGOT and total bilirubin), and specific IgE and IgG4.
Sample Size	It was planned to include 34 subjects in the DP/MG/14-2 group at dose 100/100 DPP/ml and 34 subjects in the DP/MG/14-1 group at dose 100/1000 DPP/ml. An interim safety analysis was foreseen to be performed to assess safety of the first

	18 subjects of the DP/MG/14-2 group at dose 100/1000 DPP/ml intervention and include 34 subjects at a reduced dose (DP/MG/14-2 100/500 DPP/ml). Finally, 7 subjects were included in the DP/MG/14-1 group at dose 100/1000 DPP/ml, none in the DP/MG/14-1 group at dose 100/500 DPP/ml and 33 subjects in the DP/MG/14-2 group at dose 100/100 DPP/ml. The primary endpoint (safety) was assessed in all subjects included and the secondary endpoints (efficacy) were assessed only in the DP/MG/14-2 subjects.
Selection Criteria	**Inclusion Criteria** 1. Subject provided appropriately signed and dated written informed consent. 2. Men and women aged between 18 years and 70 years (both included) of age at Visit 1. 3. Has a FEV_1 value ≥ 80% of predicted normal value at Visit 1 or Visit 2. 4. Subjects suffering from perennial allergic rhinitis or rhinoconjunctivitis moderate-severe (see study protocol Annex 8 [**Appendix 16.1.1**)] in order to verify the disease burden) for at least the preceding year, with controlled asthma, caused by double sensitization against *D. pteronyssinus* and *L. destructor* or *D. pteronyssinus* and *B. tropicalis*. 5. The IgE-mediated sensitization must be verified by the following: • Suggestive medical history, and • Specific IgE to *D. pteronyssinus* and *L. destructor* or *D. pteronyssinus* and *B. tropicalis* ≥ 0,7 KU/l (class II). The IgE results were valid if performed within one year prior to V1, and • Positive skin prick test (SPT) to *D. pteronyssinus* and *L. destructor* or *D. pteronyssinus* and *B. tropicalis*. A SPT was considered positive when it produced a wheal whose diameter was at least 3 mm. The negative control should not develop a wheal or it should be smaller than the *D. pteronyssinus* one in 3 mm. 6. Asthmatic subjects could be included in the study only if allergic asthma was controlled according to the Global Initiative for Asthma (GINA updated 2014). 7. Asthmatic subjects should be stable within 3 months prior to Visit 1 and on a stable inhaled steroid dose within 6 weeks prior to Visit 1 and throughout the study. 8. Subjects sensitized to co-allergens such as tree pollen, grasses or weeds, fungi or animal epithelials could not participate in the study if they were symptomatic. Subjects sensitized to animal dander could participate only if they are not exposed. 9. If a female was of non-childbearing potential, the subject should be postmenopausal for at least 1 year or surgically sterile (e.g., bilateral tubal ligation, bilateral oophorectomy, or hysterectomy). 10. If a female was of childbearing potential, the subject should be non-lactating and non-pregnant (with a negative pregnancy test result at Visit 1) and must correctly use an effective method of contraception during the study. An effective method of contraception was defined as one that resulted in a failure rate of less than 1% per year. The following were allowed methods of contraception when used continuously and properly: hormonal contraceptives administered by implant, injection, or orally;

	complete abstinence; partner's vasectomy if the female had no more than one partner. Barrier methods (e.g., preservatives) were only considered effective if used together with one of the above. **Exclusion Criteria** 1. Any contraindication for treatment with allergen specific immunotherapy. 2. Subjects with a previous history of anaphylaxis. 3. Subjects with hospital admission due to asthma exacerbations within 1 year prior to Visit 1. 4. Had uncontrolled asthma, according to Global Initiative for Asthma Guidelines (GINA 2014). 5. Acute or chronic infectious conjunctivitis. 6. Had acute or chronic inflammatory or infectious airways disease. 7. Has chronic structural diseases of the affected organ (e.g. eye, nose, lung). 8. History or presence of confirmed or potential diseases of the immune system including autoimmune diseases and immune deficiencies of actual clinical relevance. 9. Has any disease that prohibits the use of adrenaline (e.g., hyperthyroidism). 10. Has a severe uncontrolled disease that could increase the risk to the subjects while participating in the study, including but not limited to, the following: cardiovascular insufficiency, any severe or unstable lung diseases, endocrine diseases, clinically significant renal or hepatic diseases or hematological disorders. 11. Subjects with chronic urticaria. 12. Subjects with moderate-severe atopic dermatitis (subjects with a SCORAD value >30 could not participate in the study). 13. Had had malignant disease within the previous 5 years. 14. Had a significant abnormal laboratory parameter or alteration in vital signs that could increase the risk to the study subject. 15. Had used immunotherapy with allergenic extracts of storage or house dust mites within the last 5 years or was receiving allergen specific immunotherapy with other allergens during the study period. 16. Had used systemic and/or topical treatment with beta-blocker drugs within 1 week prior to Visit 2 (first IMP administration). 17. Used psychotropic, tricyclic, tetracyclic and MAOI antidepressants within 1 month prior to Visit 1. It will not be allowed to perform a washout period of psychotropic or antidepressants to enter the study because of the risks of interrupting the treatment. 18. Used systemic corticosteroids within 3 months prior to Visit 1. 19. Treatment with substances interfering with the immune system 2 weeks before Visit 2 (first IMP administration). 20. Immunization with prophylactic (bacterial or viral) vaccines within 7 days prior to Visit 1 and within 7 days prior to visit 2 (first IMP administration). Prophylactic vaccines were allowed during the period of IMP administration provided they were administered at least one week after immunotherapy and the next immunotherapy dose was administered at least 14 days later.

	21. Exposure to any investigational drug within one month or 6 half-lives of the drug (whichever is longer). 22. Alcohol, drugs or medications abuse within the past year prior to Visit 1. 23. Lack of cooperation or compliance. 24. Donation of germ cells, blood, organs and/or bone marrow for the duration of the study.
Endpoints	**Primary endpoints** • Subjects (%) suffering from immediate or delayed systemic ≥ grade 2 reactions, according to EAACI 2006 classification, along the study. **Secondary endpoints** • Subjects (%) suffering from immediate or delayed local reactions classified by the diameter of induration (< 5 cm, 5-10 cm o > 10 cm) and IMP received. • Subjects (%) suffering from immediate or delayed systemic reactions classified by grade (EAACI classification) and IMP received. • Subjects (%) withdrawn from the study due to local reactions classified by IMP received. • Subjects (%) withdrawn from the study due to local reactions classified by IMP received during the build-up phase. • Subjects (%) withdrawn from the study due to systemic reactions classified by IMP received. • Subjects (%) withdrawn from the study due to systemic reactions classified by IMP received during the build-up phase. • Subjects (%) with adverse events (AE) classified by IMP received. • Number of immediate or delayed local reactions classified by diameter of induration (< 5 cm, 5-10 cm o > 10 cm) and IMP received. • Number of immediate or delayed systemic reactions classified by grade (EAACI classification) and IMP received. • Change of lung function parameters before and after each administration of the IMP. • Change from baseline to Visit 4 in laboratory safety parameters. • Change in symptoms and rescue medication score from baseline to final visit. • Change in symptoms score (nasal, ocular and pulmonary symptoms) from baseline to final visit. • Change in rescue medication score from baseline to final visit. • Subjects (%) with an improvement in symptoms and rescue medication score after treatment compared to baseline. • Subjects (%) with an improvement in symptoms score after treatment compared to baseline. • Subjects (%) with an improvement in rescue medication score after treatment compared to baseline. • Change from baseline to final visit in ACQ. • Subjects (%) with an improvement in quality of life questionnaires after treatment compared to baseline. • Subjects (%) with an improvement in VAS after treatment compared to baseline.

	Exploratory immunological endpoint: Description of immunological response measured by immunological parameters (specific IgE and IgG4) after receiving the administration of the first maintenance dose at 4 weeks of starting treatment and compared to baseline values.
Statistical methods	The number of subjects (%) with at least one systemic or delayed grade ≥ 2 reaction (according to EAACI 2006 classification) along the study was analyzed using a binomial exact test. The symptom and medication scores corresponded to average of the daily score of symptom burden and use of rescue medication, respectively, during the 15 days in that the questionnaire was collected (these data were collected every 6 months). Continuous data was presented with the number of observations, mean, median, standard deviation (SD), minimum, interquartile range (IQR) and maximum. Categorical data was presented as frequencies and percentages.
Test Product, Dose, Mode of Administration, Batch Number(s)	Two IMPs were tested in this study, at different dosing: • DP/MG/14-1 (Depigoid® DUO *D. pteronyssinus/ B. tropicalis*) at 100/1000 DPP/ml and in case safety concerns were found in the first 18 subjects receiving 100/1000 DPP/ml, at 100/500 DPP/ml. Finally, only the dose 100/1000 DPP/ml was used. • DP/MG/14-2 (Depigoid® DUO *D. pteronyssinus/L. destructor*) at 100/100 DPP/ml The administration regimen consisted of a *rush* build-up regimen and a follow-up phase: • *Rush* build-up phase: On the first day of administration (Visit 2) DP/MG/14-1 or DP/MG/14-2 were administered in the form of 2 subcutaneous injections of 0.2 ml and 0.3 ml with a 30-minute interval between the two administrations. The second dose was injected only if no adverse drug reactions (ADRs) were observed 30 minutes after the first dose. Subjects remained under observation at least one hour after the last administration. • Maintenance phase: On the second day of administration (Visit 3), 0.5 ml of DP/MG/14-1 or DP/MG/14-2 were injected. This administration was repeated monthly during 23 months. Subjects remained under observation at least one hour after the last administration. Administration was subcutaneous for all IMPs.
Duration of Treatment	Total duration of treatment: 24 months.
Control Product, Dose, Mode of Administration, Batch Number(s)	Not applicable.

Summary of Results	**Safety Results Summary** • None of the 40 subjects in the Safety population experienced immediate or delayed systemic grade ≥ 2 reactions, according to EAACI 2006 classification, regardless of the IMP received. • Subjects in the Safety population experienced a total of 283 AEs, of which 8 (2.8%) and 14 (4.9%) were systemic and local reactions, experienced by 6 (15%) and 10 (25.0%) of the 40 subjects, respectively. • Immediate or delayed systemic reactions were mostly Grade I (EAACI classification) and local reactions were mostly mild (0-10 cm). • None of the subjects was withdrawn from the study due to systemic or local reactions, including those experienced during the *rush* build-up phase. However, 2 (0.7%) subjects discontinued IMP permanently, due to thrombophlebitis (n=1) and an asthma-worsening respiratory infection (n=1). • Of the 287 AEs were reported, 279 were treatment-emergent adverse events (TEAEs), and were mostly mild (n=256 [89.2%]) and moderate (n=30 [10.5%]), although one (0.3%) was severe and, additionally, serious. • Of the 279 TEAEs, 22 (7.8%) were adverse drug reactions (ADRs) (i.e., TEAE related to the IMP) experienced by 13 (32.5%) subjects and were mostly mild (n=20 [90.9%]). The most frequent ADRs were pruritus and skin reaction occurring in 4 (10%) and 3 (7.5%) subjects, respectively. The most frequent TEAEs were infections, including upper respiratory tract infection, influenza, respiratory tract infection, tooth infection, pharyngitis, and nasopharyngitis in 14 (35%), 12 (30%), 7 (17.5%), 6 (15%), 5 (12.5%) and 4 (10%) subjects respectively, nervous system disorders, including headache in 17 (42.5%) subjects, asthma in 12 (30%) subjects, skin and subcutaneous tissue disorders such as pruritus in 7 (17.5%) subjects; and musculoskeletal and connective tissue disorders such as back pain and myalgia in 4 (10%) subjects each. • No subjects died during the study period. Eight (2.9%) serious AEs were reported in 4 subjects, including ligament sprain, meniscus injury, thrombophlebitis, asthma, bronchospasm and asthma crisis. All serious AEs were TEAEs. • PEFR, measured before and 30 min after each IMP administration, significantly decreased after the second dose in V2 and the dose in V3 in the total Safety population, and the dose in V3 in subjects receiving Depigoid® DUO *D. pteronyssinus/L. destructor*, however remained within normal limits. • Laboratory safety parameters remained unchanged between baseline and the end of the safety period (at week 5 after the first IMP administration), with the exception of MCV, which significantly decreased from mean (SD) 91.7 (5.1) to 91.4 (2.7) fL in subjects receiving Depigoid® DUO *D. pteronyssinus/ B. tropicalis*. Creatinine was significantly increased at 12 months after the first IMP administration from mean (SD) 0.86 (0.11) to 0.91 (0.13) mg/dL, and it returned to baseline values by 24 months, mean (SD) 0.87 (0.10) mg/dL. **Efficacy Results Summary** • Analysis of the evolution of cSMS of subjects in the PP population, who received Depigoid® DUO *D. pteronyssinus/L. destructor*, showed that cSMS

	gradually decreased throughout the follow-up period and that changes between baseline and V6 (12 months), V7 (18 months) and V8 (24 months) were statistically significant. The frequency of subjects with decreased cSMS compared to baseline gradually increased from V5 (62.5%) to V8 (83.9%), indicating a reduction in symptoms and use of medication in most subjects from 6 months of treatment. • Analysis of the evolution of symptoms scores, including nasal, ocular, and bronchial symptoms of subjects in the PP population, receiving Depigoid® DUO *D. pteronyssinus/L. destructor*, revealed that all symptoms scores gradually decreased between baseline and during the follow-up period (V5 to V8, i.e., 6 to 24 months). Changes were statistically significant for nasal symptoms scores between baseline and V6 (12 months), V7 (18 months), and V8 (24 months), for ocular symptoms scores between baseline and V7 (18 months) and V8 (24 months), and for bronchial symptoms scores between baseline and each visit. At the last follow-up visit, all symptoms scores showed a significant decrease compared to baseline, indicating reduced symptoms after 2 years of treatment. • Overall, the frequency of subjects receiving Depigoid® DUO *D. pteronyssinus/L. destructor* with decreased symptom scores, compared to baseline scores, gradually increased throughout follow-up visits, with the exception of bronchial symptom scores, which remained similar during follow-up visits. Nevertheless, most subjects showed decreased nasal, ocular and bronchial symptom scores at each visit, with the exception of ocular symptom scores at V6 (12 months), which, in most subjects (53.6%), did not decrease. Moreover, of the total of subjects in the PP population, 74.2%, 71% and 67.7% showed decreased nasal, ocular and bronchial symptom scores, respectively, at the end of the follow-up period (V8, 24 months), indicating reduced symptoms after 2 years of treatment. • Analysis of the evolution of rescue medication scores of subjects in the PP population, who received Depigoid® DUO *D. pteronyssinus/L. destructor*, showed a gradual decrease during the follow up period, with significant changes between baseline and V6 (12 months), V7 (18 months) and V8 (24 months). • The frequency of subjects with decreased rescue medication scores increased throughout the follow-up period, indicating reduced use of rescue medication after treatment in most subjects. • Asthma Control Questionnaire scores of subjects in the PP population receiving Depigoid® DUO *D. pteronyssinus/L. destructor* showed a significant decrease between baseline and the final visit (24 months), indicating improved asthma control after 2 years of treatment. • Global score of the asthma and rhinoconjunctivitis (AQLQ) increased and global score of rhinoconjunctivitis quality of life questionnaire (RQLQ) decreased at the final visit (V8, 24 months) compared to baseline, indicating improved quality of life after 2 years of treatment. In addition, most of the questionnaires' domains improved with the exception of emotional function, included in the AQLQ, and activities, sleep, general symptoms, eye, and emotional domains, included in the RQLQ. • The frequency of subjects with increased AQLQ and decreased RQLQ global scores gradually increased during the follow-up period compared to baseline. Frequencies of subjects with increased AQLQ individual domains

	scores also increased after treatment, whereas those of RQLQ domains remained unchanged, with the exception of practical problems and eye subdomain scores. • The scores of a visual analogue scale (VAS) grading subjects' severity disease perception significantly and gradually decreased throughout follow-up visits, indicating that subjects perceived their disease as less severe after treatment. • Levels of *D. pteronyssinus* IgE remained unchanged throughout the study, whereas those of *L. destructor* experienced a transient significant increase at V4 (7 weeks). Levels of *D. pteronyssinus* and *L. destructor* sIgG4 significantly increased form baseline and during the follow-up period.
Conclusions	• Treatment with Depigoid® DUO *D. pteronyssinus/ B. tropicalis* or Depigoid® DUO *D. pteronyssinus/L. destructor* administered following a *rush* build-up regimen, showed a favorable safety profile in subjects with allergic rhinitis or rhinoconjunctivitis, with controlled asthma, lacking immediate or delayed systemic reactions of grade ≥ 2. • Treatment with Depigoid® DUO *D. pteronyssinus/ B. tropicalis* or Depigoid® DUO *D. pteronyssinus/L. destructor* administered following a *rush* build-up regimen, resulted in a low frequency of subjects experiencing immediate or delayed systemic and local reactions. Systemic reactions were mild and local reactions were mild and moderate. • None of the subjects was withdrawn from the study due to local and systemic reactions occurring during the study, including the *rush* build-up phase, regardless of the IMP received. • All subjects treated with Depigoid® DUO *D. pteronyssinus/ B. tropicalis* or Depigoid® DUO *D. pteronyssinus/L. destructor* experienced at least one AE, with the exception of one subject treated with Depigoid® DUO *D. pteronyssinus/L. destructor*. • Most AE occurring during the study were mild and moderate TEAE, of which few were adverse drug reactions, and mostly mild. • Treatment with Depigoid® DUO *D. pteronyssinus/ B. tropicalis* or Depigoid® DUO *D. pteronyssinus/L. destructor* administered following a *rush* build-up regimen, did not result in clinically relevant changes in lung function after each IMP administration, and clinically relevant changes in laboratory safety parameters during the safety phase. • Treatment with Depigoid® DUO *D. pteronyssinus/L. destructor*, administered following a *rush* build-up regimen, was effective in reducing symptom and rescue medication score, individual symptom scores, and combined rescue medications at 12, 18, and 24 months compared to baseline, showing a clinical benefit in subjects with allergic rhinitis or rhinoconjunctivitis, with controlled asthma. Nasal and ocular symptoms showed an improvement from 12 months, while bronchial symptoms started improving at 6 months from treatment start. • Most subjects treated with Depigoid® DUO *D. pteronyssinus/L. destructor* had decreased combined symptom and rescue medication score between baseline and 12, 18, and 24 months, showing improved symptoms and reduced use of rescue medication at 12 months from treatment start which was maintained after 24 months of treatment. • Treatment with Depigoid® DUO *D. pteronyssinus/L. destructor*, administered following a *rush* build-up regimen, was effective in reducing Asthma Control

	Questionnaire scores between baseline and the final visit, showing and improvement in asthma control after 24 months of treatment. • Most subjects treated with Depigoid® DUO *D. pteronyssinus/L. destructor* showed improved quality of life questionnaire scores and a perception of allergic disease as less severe after treatment. • Treatment with Depigoid® DUO *D. pteronyssinus/L. destructor* induced a transient increase in *L. destructor* IgE levels and a sustained increase of *D. pteronyssinus* and *L. destructor* sIgG4 levels between baseline and the final visit.
Date and Version of this Report	Version 1.0, date: 31/05/2021