1 TITLE PAGE

STUDY TITLE:	Prospective study to evaluate the safety of a 4-month treatment with Depigoid® *Dermatophagoides pteronyssinus* or 50% *Dermatophagoides pteronyssinus* / 50% *Dermatophagoides farinae* (500 DPP/ml) in patients with allergic rhinitis or rhinoconjunctivitis with or without mild persistent or intermittent asthma.
EudraCT NUMBER:	2011-000870-79
STUDY DRUG:	Depigoid® *D. pteronyssinus* (500 DPP/ml) Depigoid® 50% *D. pteronyssinus* / 50% *D. farinae* (500 DPP/ml)
STUDY INDICATION:	Allergic rhinitis or rhinoconjunctivitis with or without mild persistent or intermittent asthma
DESIGN:	Prospective, non-randomized, uncontrolled, open-label safety study
SPONSOR:	Laboratorios LETI, S.L.U., C/ Sol, 5, 28760 Tres Cantos, Madrid, Spain
PROTOCOL CODE:	101-PG-PSC-186 (Laboratorios LETI S.L.U.), (HCR: 1792/LET)
PHASE:	II
INITIATION:	04 June 2012, screening of first patient included in the study
COMPLETION:	31 July 2012, final examination of the last patient The study was terminated early by the sponsor.
COORDINATING INVESTIGATOR:	Not applicable.
GCP STATEMENT:	This study was performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and local legal and regulatory requirements.
ARCHIVING:	The study documents will be archived according to ICH GCP regulations.
DATE OF REPORT:	24 April 2013, Final
EARLIER REPORTS:	None.

2 SYNOPSIS

Name of Sponsor/company: Laboratorios LETI S.L.U.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Depigoid®	Volume:	
Name of Active Ingredient(s): *Dermatophagoides pteronyssinus* - 50% *Dermatophagoides pteronyssinus* / 50% *Dermatophagoides farinae*	Page:	

Title of the study:
Prospective study to evaluate the safety of a 4-month treatment with Depigoid® *Dermatophagoides pteronyssinus* or 50% *Dermatophagoides pteronyssinus* / 50% *Dermatophagoides farinae* (500 DPP/ml) in patients with allergic rhinitis or rhinoconjunctivitis with or without mild persistent or intermittent asthma.

Investigators:
Dra. Victoria Cardona (site 1), Dr. Alfons Malet (site 3), Dr. Francisco Moreno (site 6),
Dr. Josep Mª Torres Rodríguez (site 10)
No patients recruited:
Dra. Mercè Corominas (site 2), Dr. Pere Gaig (site 4), Dr. Angel Julio Huertas (site 5), Dr. Fernando Rodríguez (site 7), Dra. Teresa Carrillo Díaz (site 8), Dr. José Amat (site 9)

Study centre(s):
Site 1: H. U. Vall d'Hebron, Secció d´Al.lergologia, 2ªplanta Edifici Antiga Escola Infermeria, Pg. Vall d'Hebron, 119-129, 08035 Barcelona, Spain
Site 3: Al·lergo Centre, C/ Laforja, 95 (pral), 08021 Barcelona, Spain
Site 6: Clínica Dr. Lobatón, Cádiz, Avda. Fernández Ladreda, 9, 11008 Cádiz, Spain
Site 10: Centro Médico Teknon, Unidad de Alergia Consultorios Marquesa (despacho 32), Marquesa de Vilallonga, 12, 08017 Barcelona, Spain
No patients recruited:
Site 2: Hospital de Bellvitge, Edificio de Consultas Externas., Planta 2, Módulo 21, C/Feixa Llarga, S/N, 08907 L'Hospitalet de Llobregat, Spain
Site 4: Hospital Joan XXIII, Dr. Mallafré i Guasch, 4, 43007 Tarragona, Spain
Site 5: Complejo Hospitalario Universitario de Cartagena, H.U Santa María del Rosell Servicio de Alergia 3ª planta A, Paseo de Alfonso XIII, 61 30203 Cartagena, Spain
Site 7: Hospital Marqués de Valdecilla, Consultas de Alergia, Edificio Valdecilla Sur 2ªplanta, Av. Marqués de Valdecilla s/n, 39008 Santander, Spain
Site 8: Servicio de Alergología. Planta 4, sector D, Hospital Universitario de Gran Canaria Dr. Negrin, Barranco de la Ballena s/n, 35016 Las Palmas de Gran Canaria, Spain
Site 9: Hospital Torrecárdenas, Paraje Torrecárdenas s/n., 04009. Almería, Spain

Publication:
Not applicable

Study period:	**Phase of Development:**
04 June 2012 (first enrolment) 31 July 2012 (last completed)	II

Objectives:

Primary objective: to evaluate the safety of a 4-month treatment with an extract of Depigoid® *Dermatophagoides pteronyssinus* or a mixture of 50% *Dermatophagoides pteronyssinus* and 50% *Dermatophagoides farinae* at a concentration of 500 DPP/ml administered following a rush build-up regimen.

Secondary objective: to assess the subjects' immunologic responses to the above treatment.

Methodology:

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This was a prospective, non-randomized, uncontrolled, open-label safety study in subjects with allergic rhinitis or rhinoconjunctivitis, with or without mild persistent or intermittent allergic asthma, who were sensitized to house dust mites.

It was planned that a total of 103 adult subjects received subcutaneous allergen-specific immunotherapy at 10 study centers (allergy services) in Spain. However, the clinical study was prematurely terminated by the sponsor in order to preserve the subjects' safety due to an unexpected high incidence of delayed adverse reactions in 5 out of the 7 patients included in the clinical trial.

Depending on their sensitization to house dust mites, the subjects received either Depigoid® *Dermatophagoides pteronyssinus* (500 DPP/ml) or Depigoid® mite mix (50% *D. pteronyssinus* and 50% *D. farinae;* 500 DPP/ml). The first two doses (0.2 ml and 0.3 ml) were administered at a 30-min interval (rush build-up regimen). It was planned that the subsequent 4-month maintenance regimen consisted of monthly injections of 0.5 ml.

The first administration of study medication was preceded by a 1-week wash-out period (during which a number of pre-specified treatments were not allowed), the last dose was to be followed by a 1-week follow-up period. It was planned that during the treatment period visits would be conducted every 4 weeks (± 7 d). After administration of the study medication, the subjects remained at the study center under the supervision of the study personnel for at least 1 h; 24 h after the administration, they were contacted by telephone and asked about the occurrence of delayed local or systemic reactions.

Number of subjects:

Planned: 103 subjects in total

Analyzed: 7 subjects

Main criteria for inclusion:

Inclusion:

- Men and women between 18 and 55 years of age (both inclusive).
- Individuals suffering symptoms of allergic rhinoconjunctivitis or rhinitis during at least the preceding year -- with or without symptoms of mild persistent or intermittent allergic asthma which is controlled with a dose ≤ 400 µg/day Budesonide or an equivalent -- caused by a clinically relevant sensitization to house dust mites (*Dermatophagoides pteronyssinus* or *Dermatophagoides pteronyssinus and Dermatophagoides farinae*).
  The IgE-mediated sensitization will be demonstrated by means of the following tests: specific IgE to house dust mites (*D. pteronyssinus* or *D. pteronyssinus and D. farinae*) CAP RAST ≥ 2 and positive skin prick test. A skin prick test will be considered positive when it produces a wheal of at least 3 mm according to the largest diameter.
  Asthmatic patients must be stable and on a stable inhaled steroid dose within 6 weeks prior to visit 1 and throughout the study.

Exclusion:

- Any contraindication for treatment with allergen specific immunotherapy.
- FEV1 or PEF value < 80% of the predicted normal value.
- Allergy symptoms due to sensitization to pollens or other perennial allergens (molds, epithelia).

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Test product, dose and mode of administration, batch number:

Depigoid® *D. pteronyssinus* (500 DPP/ml, batch no. F-7) or

Depigoid® 50% *D. pteronyssinus* / 50% *D. farinae* (500 DPP/ml, batch no. F-8)

Dose: Week 0: 0.2 ml followed by 0.3 ml after 30 min
(Week 4, 8, 12, and 16: 0.5 ml, not administered due to premature termination of the study)

Mode of administration: subcutaneous injection

Duration of treatment:

Planned: 16 weeks

Study was prematurely terminated.

Reference therapy, dose and mode of administration, batch number:

Not applicable.

Criteria for evaluation:

Efficacy:

Immunologic response to the treatment was not assessed because the study was prematurely terminated.

Safety:

Adverse events (AEs), immediate or delayed adverse drug reactions (ADRs), physical examination, vital signs, spirometry, pregnancy test

Statistical methods:

Not applicable.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Not applicable.

SAFETY RESULTS:

The study was prematurely terminated as the ADRs indicated a possible risk for the health of patients participating in the clinical trial. This decision was taken by the sponsor in order to safeguard subject safety.

CONCLUSION:

A total of seven patients with allergic rhinitis or rhinoconjunctivitis with or without mild persistent or intermittent asthma received the first two doses (0.2 ml and 0.3 ml at a 30-min interval) of Depigoid® *Dermatophagoides pteronyssinus* or 50% *Dermatophagoides pteronyssinus* / 50% *Dermatophagoides farinae* (500 DPP/ml) in this study.

The study was prematurely terminated due to an unexpected high incidence of delayed adverse reactions in five of the seven patients treated with the study medication. The study protocol included in its section 5.3.3.2 specific reasons for early termination:

- A grade-4 systemic reaction (2006 EAACI classification) observed in a study subject.
- If the planned interim analysis had shown any of the assumptions described.

None of the before mentioned situations occurred, but it was also pre-specified in the study protocol that the sponsor reserved the right to modify or terminate the study at any time due to safety reasons; particularly when the incidence of adverse events in this study or any other with the same medicinal product indicated a possible higher risk for patient´s safety.

The causal relationship between adverse reactions that occurred and the study medication administered was considered as "related", by both the investigators in the study and Laboratorios LETI, S.L.U. None of the reactions was considered as "serious" from the regulatory point of view.

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<tr><td colspan="3">Further investigations are required before additional administration of the medicinal product at 500 DPP/ml, as tested in this clinical trial, takes place.</td></tr>
<tr><td colspan="3">Date of the report: 24 April 2013</td></tr>
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