



## Clinical trial results:

**Open multicenter clinical trial to confirm the maximum no reactive dose of allergoid of polymerized Dermatophagoides pteronyssinus, in patients with allergic rhinoconjunctivitis or mild or moderate asthma, who are sensitive to Dermatophagoides pteronyssinus**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2014-004429-42  |
| Trial protocol           | ES              |
| Global end of trial date | 07 October 2015 |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 26 January 2019 |
| First version publication date | 26 January 2019 |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | DIA-Der-02-14 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN)   | - |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Diater Laboratorio de Diagnóstico y Aplicaciones Terapéuticas, S.A.  |
| Sponsor organisation address | Avenida Gregorio Peces Barba, 2, Leganes / Madrid, Spain, 28918  |
| Public contact               | Medical department, Diater Laboratorio de Diagnósticos y Aplicaciones Terapéuticas, S.A., 0034 914966013, departamento.medico@diater.com |
| Scientific contact           | Medical Department, Diater Laboratorio de Diagnósticos y Aplicaciones Terapéuticas, S.A., 0034 914966013, departamento.medico@diater.com |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

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**Results analysis stage**

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|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 30 May 2016     |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 07 October 2015 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 07 October 2015 |
| Was the trial ended prematurely?                     | No              |

Notes:

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**General information about the trial**

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Main objective of the trial:

To confirm the maximum non- reactive dose of Polymerized Dermatophagoides pteronyssinus, administered intradermally

Protection of trial subjects:

subjects should stay under medical surveillance in the center at least 60 minutes after drug administration . Additionally subjects received a telephone call from the investigator team 24 hours later the administration to register and assess any potential late adverse event

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 04 May 2015 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 40 |
| Worldwide total number of subjects   | 40        |
| EEA total number of subjects         | 40        |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 40 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

all patients recruited completed the study

### Pre-assignment

Screening details:

Positive levels of IgE antibodies against Dermatophagoides pteronyssinus in the previous year to inclusion was considered valid.

Wash-out period for : Antihistamines: 7 days. Short-acting beta-2 adrenergics: 4 hours. Long-acting beta-2 adrenergics: 12 hours. Antileukotrienes: 24 hours, inhaled corticosteroids: 12 hours, chromones: 24 hours

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

Blinding implementation details:

Given that all efficacy study endpoints are objectively measured and can not be modified by either subject or investigator, blinding was considered not necessary for this study.

### Arms

|           |           |
|-----------|-----------|
| Arm title | Der p pol |
|-----------|-----------|

Arm description:

Polymerized Dermatophagoides pteronyssinus at 4 different doses: 0.001, 0.01, 0.1 and 1 mg/ml

|  |   |
|--|---|
| Arm type                               | Experimental                                  |
| Investigational medicinal product name | Polymerized Dermatophagoides pteronyssinus    |
| Investigational medicinal product code | Der p pol                                     |
| Other name                             |   |
| Pharmaceutical forms                   | Powder and solvent for solution for injection |
| Routes of administration               | Intradermal use                               |

Dosage and administration details:

4 different concentrations (0.001, 0.01, 0.1 and 1 mcg/mL) of the IMP was administered to each single patient. Dose of each concentration was 0.1 ml

|                                       |           |
|---------------------------------------|-----------|
| <b>Number of subjects in period 1</b> | Der p pol |
| Started                               | 40        |
| Completed                             | 40        |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | overall trial |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values                             | overall trial | Total |  |
|--|---------------|-------|--|
| Number of subjects                                 | 40            | 40    |  |
| Age categorical                                    |               |       |  |
| Units: Subjects                                    |               |       |  |
| In utero   | 0             | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                               | 0             | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0             | 0     |  |
| Children (2-11 years)                              | 0             | 0     |  |
| Adolescents (12-17 years)                          | 0             | 0     |  |
| Adults (18-64 years)                               | 40            | 40    |  |
| From 65-84 years                                   | 0             | 0     |  |
| 85 years and over                                  | 0             | 0     |  |
| Age continuous                                     |               |       |  |
| Units: years                                       |               |       |  |
| arithmetic mean                                    | 28.38         |       |  |
| standard deviation                                 | ± 7.86        | -     |  |
| Gender categorical                                 |               |       |  |
| Units: Subjects                                    |               |       |  |
| Female   | 23            | 23    |  |
| Male   | 17            | 17    |  |
| Study disease                                      |               |       |  |
| Units: Subjects                                    |               |       |  |
| Rhinitis and/or Rhinoconjunctivitis with asthma    | 32            | 32    |  |
| Rhinitis/Rhinconjunctivitis w/ asthma not reported | 8             | 8     |  |

### Subject analysis sets

|                            |              |
|----------------------------|--------------|
| Subject analysis set title | Per protocol |
|----------------------------|--------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

The statistical acceptance criteria for eligible subjects are:

\* A regression line of at least 3 concentrations with a correlation coefficient > 0.85.

\* A slope of the regression line > 0.1.

\* Values obtained after regression within the concentration values used.

|                            |                |
|----------------------------|----------------|
| Subject analysis set title | ITT population |
|----------------------------|----------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

all enrolled subjects receiving at least 3 out of 4 drug concentration tested

| Reporting group values                                 | Per protocol | ITT population |  |
|--|--------------|----------------|--|
| Number of subjects                                     | 17           | 40             |  |
| Age categorical  |              |                |  |
| Units: Subjects  |              |                |  |
| In utero   | 0            | 0              |  |
| Preterm newborn infants<br>(gestational age < 37 wks)  | 0            | 0              |  |
| Newborns (0-27 days)                                   | 0            | 0              |  |
| Infants and toddlers (28 days-23<br>months)            | 0            | 0              |  |
| Children (2-11 years)                                  | 0            | 0              |  |
| Adolescents (12-17 years)                              | 0            | 0              |  |
| Adults (18-64 years)                                   | 17           | 40             |  |
| From 65-84 years                                       | 0            | 0              |  |
| 85 years and over                                      | 0            | 0              |  |
| Age continuous   |              |                |  |
| Units: years   |              |                |  |
| arithmetic mean  | 29.71        | 28.38          |  |
| standard deviation                                     | ± 8.53       | ± 7.86         |  |
| Gender categorical                                     |              |                |  |
| Units: Subjects  |              |                |  |
| Female   | 10           | 23             |  |
| Male   | 7            | 17             |  |
| Study disease  |              |                |  |
| Units: Subjects  |              |                |  |
| Rhinitis and/or Rhinoconjunctivitis<br>with asthma     | 15           |                |  |
| Rhinitis/Rhinoconjunctivitis w/<br>asthma not reported | 2            |                |  |

## End points

### End points reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | Der p pol          |
| Reporting group description:   |                    |
| Polymerized Dermatophagoides pteronissynuss at 4 different doses: 0.001 , 0.01 , 0.1 and 1 mg/ml |                    |
| Subject analysis set title   | Per protocol       |
| Subject analysis set type  | Per protocol       |
| Subject analysis set description:  |                    |
| The statistical acceptance criteria for eligible subjects are:                                   |                    |
| * A regression line of at least 3 concentrations with a correlation coefficient > 0.85.          |                    |
| * A slope of the regression line > 0.1.  |                    |
| * Values obtained after regression within the concentration values used.                         |                    |
| Subject analysis set title   | ITT population     |
| Subject analysis set type  | Intention-to-treat |
| Subject analysis set description:  |                    |
| all enrolled subjects receiving at least 3 out of 4 drug concentration tested                    |                    |

### Primary: Maximum non-reactive drug concentration

|   |  |
|---|--|
| End point title   | Maximum non-reactive drug concentration <sup>[1]</sup> |
| End point description:  |  |
| Maximum non-reactive drug concentration was defined as those concentration inducing a largest wheal diameter equal to 2.9 mm  |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| Immediately after administration, and 15 minutes after. Largest wheal diameter was calculated by subtracting the initial wheal induced to the final wheal obtained. In the case of obtaining a wheal with the negative control (manitol) it was also subtracted |  |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analyses as required (p-values for group comparisons) is not applicable to calculate the primary endpoint of this study. Instead, a regression line was calculated using the logarithmic values (logarithm to base 10) of the largest wheal size from the 4 IMP doses tested. The logarithmic concentration value inducing a wheal equal to 2.9 mm was calculated by interpolation. This value was thereafter converted into a non-logarithmic value to obtain the final non-reactive concentration

|                                      |                      |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| <b>End point values</b>              | Per protocol         |  |  |  |
| Subject group type                   | Subject analysis set |  |  |  |
| Number of subjects analysed          | 17                   |  |  |  |
| Units: mcg/mL                        |                      |  |  |  |
| arithmetic mean (standard deviation) | 0.1 (± 0.1)          |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: flare of the wheal

|                 |                    |
|-----------------|--------------------|
| End point title | flare of the wheal |
|-----------------|--------------------|

End point description:

Erythema induced by the non-reactive concentration

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Time of administration and 15 minutes after. Largest erythema diameter was calculated by subtracting the initial wheal induced to the final value obtained . in the case of obtaining an erythema with the negative control (manitol), it was also subtracted

| End point values                     | Per protocol         |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| Subject group type                   | Subject analysis set |  |  |  |
| Number of subjects analysed          | 17                   |  |  |  |
| Units: mm                            |                      |  |  |  |
| arithmetic mean (standard deviation) | 30 (± 8.96)          |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: baseline Specific IgE antibodies to native extract

|                 |  |
|-----------------|--|
| End point title | baseline Specific IgE antibodies to native extract |
|-----------------|--|

End point description:

serologic values

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

IgE values were calculated at baseline visit

| End point values                     | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: kU/L                          |                      |                      |  |  |
| arithmetic mean (standard deviation) | 32.64 (± 35.84)      | 28.41 (± 30.41)      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Final Specific IgE antibodies to native extract

|                 |   |
|-----------------|---|
| End point title | Final Specific IgE antibodies to native extract |
|-----------------|---|

End point description:

serologic values

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:<br>values measured at 30-day follow-up after single drug administration |           |

| End point values                     | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: kU/L                          |                      |                      |  |  |
| arithmetic mean (standard deviation) | 31.33 (± 35.70)      | 28.08 (± 30.97)      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Baseline Specific IgG4 antibodies to native extract

|  |   |
|--|---|
| End point title                            | Baseline Specific IgG4 antibodies to native extract |
| End point description:<br>serologic values |   |
| End point type                             | Secondary   |
| End point timeframe:<br>baseline visit     |   |

| End point values                     | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: mgA/L                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 0.64 (± 0.73)        | 0.57 (± 0.53)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Final Specific IgG4 antibodies to native extract

|  |  |
|--|--|
| End point title  | Final Specific IgG4 antibodies to native extract |
| End point description:<br>serologic values                         |  |
| End point type   | Secondary  |
| End point timeframe:<br>Measured at final visit (30-day follow-up) |  |



| End point values                     | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: mgA/L                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 0.65 ( $\pm$ 0.85)   | 0.56 ( $\pm$ 0.59)   |  |  |

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Baseline Specific IgE antibodies to Der p 1

|   |   |
|---|---|
| End point title                                   | Baseline Specific IgE antibodies to Der p 1 |
| End point description:<br>serologic values        |   |
| End point type                                    | Secondary                                   |
| End point timeframe:<br>Measure at baseline visit |   |

| End point values                     | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: kU/L                          |                      |                      |  |  |
| arithmetic mean (standard deviation) | 18.1 ( $\pm$ 26.91)  | 15.17 ( $\pm$ 23.44) |  |  |

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Final Specific IgE antibodies to Der p 1

|  |  |
|--|--|
| End point title  | Final Specific IgE antibodies to Der p 1 |
| End point description:<br>serologic values                         |  |
| End point type   | Secondary                                |
| End point timeframe:<br>Measured at final visit (30-day follow-up) |  |

| End point values                     | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: kU/L                          |                      |                      |  |  |
| arithmetic mean (standard deviation) | 18.54 (± 28.56)      | 15.29 (± 24.29)      |  |  |

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Baseline Specific IgG4 antibodies to Der p 1

|  |  |
|--|--|
| End point title                            | Baseline Specific IgG4 antibodies to Der p 1 |
| End point description:<br>serologic values |  |
| End point type                             | Secondary                                    |
| End point timeframe:<br>baseline visit     |  |

| End point values                     | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: mgA/L                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 0.17 (± 0.20)        | 0.14 (± 0.14)        |  |  |

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Final Specific IgG4 antibodies to Der p 1

|  |   |
|--|---|
| End point title  | Final Specific IgG4 antibodies to Der p 1 |
| End point description:<br>serologic values             |   |
| End point type   | Secondary                                 |
| End point timeframe:<br>final visit (30-day follow-up) |   |

| End point values                     | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: mgA/L                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 0.17 ( $\pm$ 0.23)   | 0.13 ( $\pm$ 0.16)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Baseline Specific IgE antibodies to Der p 2

|   |   |
|---|---|
| End point title                           | Baseline Specific IgE antibodies to Der p 2 |
| End point description:                    |   |
| End point type                            | Secondary                                   |
| End point timeframe:                      |   |
| baseline visit before drug administration |   |

| End point values                     | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: kU/L                          |                      |                      |  |  |
| arithmetic mean (standard deviation) | 21.04 ( $\pm$ 28.24) | 19.27 ( $\pm$ 25.00) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Final Specific IgE antibodies to Der p 2

|  |  |
|--|--|
| End point title  | Final Specific IgE antibodies to Der p 2 |
| End point description:   |  |
| End point type   | Secondary                                |
| End point timeframe:   |  |
| values measured at 30-day follow-up after single drug administration |  |

| End point values                     | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: kU/L                          |                      |                      |  |  |
| arithmetic mean (standard deviation) | 21.60 ( $\pm$ 29.68) | 19.56 ( $\pm$ 25.85) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Baseline Specific IgG4 antibodies to Der p 2

|  |  |
|--|--|
| End point title                              | Baseline Specific IgG4 antibodies to Der p 2 |
| End point description:                       |  |
| End point type                               | Secondary                                    |
| End point timeframe:                         |  |
| At baseline visit before drug administration |  |

| End point values                     | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: mgA/L                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 0.17 ( $\pm$ 0.23)   | 0.16 ( $\pm$ 0.20)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Final Specific IgG4 antibodies to Der p 2

|  |   |
|--|---|
| End point title  | Final Specific IgG4 antibodies to Der p 2 |
| End point description:   |   |
| End point type   | Secondary                                 |
| End point timeframe:   |   |
| values measured at 30-day follow-up after single drug administration |   |

| <b>End point values</b>              | Per protocol         | ITT population       |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 17                   | 40                   |  |  |
| Units: mgA/L                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 0.16 (± 0.20)        | 0.16 (± 0.19)        |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

1 month after study drug administration

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Adverse event reporting additional description:

The occurrence of adverse events was to be sought by non-directive questioning of the patient at each visit including 1 phone interview 24 hours after treatment administration. Adverse events also could have been detected when they were volunteered by the patient during or between visits or through physical examination or other assessment

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|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

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### Dictionary used

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|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

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|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

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Frequency threshold for reporting non-serious adverse events: 5 %

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### Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: this is a short- duration study , with a small number of subjects required and a single intradermal drug dose administration . Neither related (local or systemic reactions) nor unrelated adverse events were reported in this study

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported