



## Clinical trial results: Immunomonitoring of tacrolimus in healthy volunteers Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2018-001775-20 |
| Trial protocol           | NL             |
| Global end of trial date | 21 August 2018 |

### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)  |
| This version publication date     | 23 March 2022   |
| First version publication date    | 23 March 2022   |
| Summary attachment (see zip file) | M3. CHDR1644_Manuscript_30Jul2019 (M3. CHDR1644_Manuscript_30Jul2019.pdf) |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | CHDR1644 |
|-----------------------|----------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Centre for Human Drug Research  |
| Sponsor organisation address | Zernikedreef 8, Leiden, Netherlands, 2333 CL  |
| Public contact               | Principal Investigator, Centre for Human Drug Research, +31 715246400, clintrials@chdr.nl |
| Scientific contact           | Principal Investigator, Centre for Human Drug Research, +31 715246400, clintrials@chdr.nl |

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:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 09 May 2019    |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 21 August 2018 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 21 August 2018 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the pharmacokinetic profile of a single dose of tacrolimus;

- o Whole blood concentrations
- o Cellular concentrations (T cells and/or PBMCs)
- o Relationship between whole blood and cellular concentrations

To investigate the pharmacodynamic effects of a single dose of tacrolimus;

- o Calcineurin activity
- o T cell function (activation, proliferation)

To investigate the relationship between the pharmacokinetic profile of tacrolimus (in whole blood and intracellular) and the pharmacodynamic effects ex vivo;

To investigate the correlation between pharmacodynamic effects (calcineurin activity and T cell function) in vitro and ex vivo;

Protection of trial subjects:

No medical benefit was expected from this study for the participating subjects.

The study drug is a registered medicinal product for the prevention of prophylaxis of the transplanted organ in transplantation patients, and has been used before in many healthy volunteer studies. All study drug administrations were done in the clinic under medical supervision. The subjects that received the study drug remained in the clinic for at least 7 hours after the study drug administration for the subjects to be closely monitored for any adverse signs during the treatment.

Background therapy: -

Evidence for comparator:

No comparator.

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 13 June 2018 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 12 |
| Worldwide total number of subjects   | 12              |
| EEA total number of subjects         | 12              |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                      | 12 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment from 13-Jun2018 – 11-Aug-2018. Location: Netherlands

### Pre-assignment

Screening details:

Healthy male or female subjects, 18-55 years of age (inclusive), without evidence of any active or chronic illness or any clinically significant abnormalities in laboratory test results, ECG and blood pressure.

### Period 1

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

### Arms

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Healthy volunteers (active) |
|------------------|-----------------------------|

Arm description:

Twelve treated subjects (0.05 mg/kg Prograf (Tacrolimus)), no placebo.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Prograf      |
| Investigational medicinal product code |              |
| Other name                             | Tacrolimus   |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

A single oral dose of 0.05 mg/kg Prograf (rounded to available dosage forms) with a glass of water.

|                                       |                             |
|---------------------------------------|-----------------------------|
| <b>Number of subjects in period 1</b> | Healthy volunteers (active) |
| Started                               | 12                          |
| Completed                             | 12                          |

## Baseline characteristics

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### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Overall period |
|-----------------------|----------------|

Reporting group description: -

| Reporting group values              | Overall period | Total |  |
|-------------------------------------|----------------|-------|--|
| Number of subjects                  | 12             | 12    |  |
| Age categorical                     |                |       |  |
| Healthy subjects 18-55 years of age |                |       |  |
| Units: Subjects                     |                |       |  |
| Adults (18-64 years)                | 12             | 12    |  |
| Gender categorical                  |                |       |  |
| Units: Subjects                     |                |       |  |
| Female                              | 6              | 6     |  |
| Male                                | 6              | 6     |  |

## End points

### End points reporting groups

|  |                             |
|--|-----------------------------|
| Reporting group title  | Healthy volunteers (active) |
| Reporting group description:<br>Twelve treated subjects (0.05 mg/kg Prograf (Tacrolimus)), no placebo. |                             |

### Primary: Tacrolimus concentration

|                        |   |
|------------------------|---|
| End point title        | Tacrolimus concentration <sup>[1]</sup> |
| End point description: |   |

|   |         |
|---|---------|
| End point type  | Primary |
| End point timeframe:<br>Pre-dose and 1.5, 48, 96 and 192 hours after drug administration. |         |

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: See uploaded article for results, endpoints and analyses.

| End point values                     | Healthy volunteers (active) |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 12                          |  |  |  |
| Units: microgram(s)/litre            |                             |  |  |  |
| arithmetic mean (standard deviation) | 21.468 ( $\pm$ 6.16)        |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From screening (up to 42 days pre-dose) until follow-up visit (7 days post-dose).

Adverse event reporting additional description:

Adverse events were investigated by the investigator routinely on all study visits and AE intensity, relationship to study intervention, chronicity and eventual actions related to the AE were determined.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | Active |
|-----------------------|--------|

Reporting group description:

Subjects treated with 0.05 mg/kg Prograf (tacrolimus)

| Serious adverse events                            | Active         |  |  |
|---|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 0 / 12 (0.00%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | Active          |  |  |
|---|-----------------|--|--|
| Total subjects affected by non-serious adverse events |                 |  |  |
| subjects affected / exposed                           | 5 / 12 (41.67%) |  |  |
| Vascular disorders                                    |                 |  |  |
| Presyncope  |                 |  |  |
| subjects affected / exposed                           | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                                     | 1               |  |  |
| Nervous system disorders                              |                 |  |  |
| Headache  |                 |  |  |
| subjects affected / exposed                           | 4 / 12 (33.33%) |  |  |
| occurrences (all)                                     | 4               |  |  |
| Respiratory, thoracic and mediastinal disorders       |                 |  |  |

|   |  |  |  |
|---|--|--|--|
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 12 (8.33%)<br>1                            |  |  |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)   | 1 / 12 (8.33%)<br>1                            |  |  |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)  | 1 / 12 (8.33%)<br>1                            |  |  |
| Musculoskeletal and connective tissue disorders<br>Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1<br><br>1 / 12 (8.33%)<br>1 |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment                 |
|--------------|---------------------------|
| 12 July 2018 | Increase of blood volume. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31547590>