



## Clinical trial results:

### Plasma kinetics for tablet and liquid formulations of 6-mercaptopurine in childhood acute lymphoblastic leukemia

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-001236-21 |
| Trial protocol           | DK             |
| Global end of trial date | 27 March 2018  |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 01 January 2021 |
| First version publication date | 01 January 2021 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | 2008-003235-20 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01906671 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                           |
|------------------------------|-------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Rigshospitalet                                                                            |
| Sponsor organisation address | Blegdamsvej 9, Copenhagen, Denmark, 2100                                                  |
| Public contact               | Clinical Trial information, Kjeld Schmiegelow, +45 35451357, Kjeld.Schmiegelow@regionh.dk |
| Scientific contact           | Clinical Trial information, Kjeld Schmiegelow, +45 35451357, Kjeld.Schmiegelow@regionh.dk |

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                       | 28 April 2020 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 27 March 2018 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 27 March 2018 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this trial is to investigate whether previous findings, from a trial conducted on healthy adults regarding plasma kinetics and bioavailability of tablet (Puri-Nethol) and oral liquid formulation (Xaluprine) of 6-mercaptopurine, is similar in the target population, children with ALL.

Protection of trial subjects:

Patients were examined in a well known and safe environment, and ingested 6-mercaptopurine, which is part of their normal treatment for acute lymphoblastic leukemia

Background therapy:

Children diagnosed with acute lymphoblastic leukemia are treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol, where 6-mercaptopurine comprises one of two cornerstones of maintenance therapy. In this trial we aimed to compare pharmacokinetics of tablet and liquid formulations of 6-mercaptopurine, which is thus a normal part of these childrens' treatment.

Evidence for comparator:

A comparative pharmacokinetic study in healthy adults demonstrated bioequivalence between tablet and liquid formulation of 6-mercaptopurine, we aimed to explore this in the target population, children with acute lymphoblastic leukemia

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 24 June 2013 |
| 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 | Denmark: 17 |
| Worldwide total number of subjects   | 17          |
| EEA total number of subjects         | 17          |

Notes:

### Subjects enrolled per age group

|                                           |    |
|-------------------------------------------|----|
| 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)                     | 16 |

|                           |   |
|---------------------------|---|
| Adolescents (12-17 years) | 1 |
| Adults (18-64 years)      | 0 |
| From 65 to 84 years       | 0 |
| 85 years and over         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Clinical examination, and receiving maintenance therapy according to Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol

### Pre-assignment

Screening details:

Clinical examination

Receiving maintenance therapy according to the NOPHO ALL2008 protocol

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Purinethol                  |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|                                        |                                                 |
|----------------------------------------|-------------------------------------------------|
| Arm title                              | Purinethol (tablet version of 6-mercaptopurine) |
| Arm description: -                     |                                                 |
| Arm type                               | Regular treatment                               |
| Investigational medicinal product name | 6-mercaptopurine                                |
| Investigational medicinal product code |                                                 |
| Other name                             | Puri-nethol                                     |
| Pharmaceutical forms                   | Tablet                                          |
| Routes of administration               | Oral use                                        |

Dosage and administration details:

According to the child's therapeutic 6-mercaptopurine dose

| Number of subjects in period 1 | Purinethol (tablet version of 6-mercaptopurine) |
|--------------------------------|-------------------------------------------------|
| Started                        | 17                                              |
| Completed                      | 16                                              |
| Not completed                  | 1                                               |
| Consent withdrawn by subject   | 1                                               |

### Period 2

|                              |                             |
|------------------------------|-----------------------------|
| Period 2 title               | Xaluprine                   |
| Is this the baseline period? | No                          |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|                                        |                                                    |
|----------------------------------------|----------------------------------------------------|
| <b>Arm title</b>                       | Xaluprine (liquid formulation of 6-mercaptopurine) |
| Arm description: -                     |                                                    |
| Arm type                               | Experimental                                       |
| Investigational medicinal product name | 6-mercaptopurine                                   |
| Investigational medicinal product code |                                                    |
| Other name                             | Xaluprine                                          |
| Pharmaceutical forms                   | Oral liquid                                        |
| Routes of administration               | Oral use                                           |

Dosage and administration details:

According to the child's therapeutic 6-mercaptopurine dose

|                                       |                                                    |
|---------------------------------------|----------------------------------------------------|
| <b>Number of subjects in period 2</b> | Xaluprine (liquid formulation of 6-mercaptopurine) |
| Started                               | 16                                                 |
| Completed                             | 16                                                 |

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Purinethol |
|-----------------------|------------|

|                                |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

| Reporting group values                    | Purinethol | Total |  |
|-------------------------------------------|------------|-------|--|
| Number of subjects                        | 17         | 17    |  |
| Age categorical                           |            |       |  |
| Units: Subjects                           |            |       |  |
| Children (2-11 years)                     | 16         | 16    |  |
| Adolescents (12-17 years)                 | 1          | 1     |  |
| Gender categorical                        |            |       |  |
| Units: Subjects                           |            |       |  |
| Female                                    | 8          | 8     |  |
| Male                                      | 9          | 9     |  |
| Diagnosis of acute lymphoblastoc leukemia |            |       |  |
| Units: Subjects                           |            |       |  |
| ALL                                       | 17         | 17    |  |

### Subject analysis sets

|                            |               |
|----------------------------|---------------|
| Subject analysis set title | Full analysis |
|----------------------------|---------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

|                                   |
|-----------------------------------|
| Subject analysis set description: |
|-----------------------------------|

|                                                 |
|-------------------------------------------------|
| Full analysis of all pharmacokinetic parameters |
|-------------------------------------------------|

| Reporting group values                    | Full analysis |  |  |
|-------------------------------------------|---------------|--|--|
| Number of subjects                        | 16            |  |  |
| Age categorical                           |               |  |  |
| Units: Subjects                           |               |  |  |
| Children (2-11 years)                     | 15            |  |  |
| Adolescents (12-17 years)                 | 1             |  |  |
| Gender categorical                        |               |  |  |
| Units: Subjects                           |               |  |  |
| Female                                    | 8             |  |  |
| Male                                      | 8             |  |  |
| Diagnosis of acute lymphoblastoc leukemia |               |  |  |
| Units: Subjects                           |               |  |  |
| ALL                                       | 16            |  |  |

## End points

### End points reporting groups

|                                                 |                                                    |
|-------------------------------------------------|----------------------------------------------------|
| Reporting group title                           | Purinethol (tablet version of 6-mercaptopurine)    |
| Reporting group description: -                  |                                                    |
| Reporting group title                           | Xaluprine (liquid formulation of 6-mercaptopurine) |
| Reporting group description: -                  |                                                    |
| Subject analysis set title                      | Full analysis                                      |
| Subject analysis set type                       | Full analysis                                      |
| Subject analysis set description:               |                                                    |
| Full analysis of all pharmacokinetic parameters |                                                    |

### Primary: Pharmacokinetic parameters, AUC, Cmax, Tmax, t<sub>1/2</sub>

|                                       |                                                               |
|---------------------------------------|---------------------------------------------------------------|
| End point title                       | Pharmacokinetic parameters, AUC, Cmax, Tmax, t <sub>1/2</sub> |
| End point description:                |                                                               |
| End point type                        | Primary                                                       |
| End point timeframe:                  |                                                               |
| On blood samples taken on study days. |                                                               |

| End point values            | Purinethol<br>(tablet version<br>of 6-<br>mercaptopurine) | Xaluprine<br>(liquid<br>formulation of<br>6-<br>mercaptopurine) | Full analysis        |  |
|-----------------------------|-----------------------------------------------------------|-----------------------------------------------------------------|----------------------|--|
| Subject group type          | Reporting group                                           | Reporting group                                                 | Subject analysis set |  |
| Number of subjects analysed | 16                                                        | 16                                                              | 16                   |  |
| Units: nmol/L               |                                                           |                                                                 |                      |  |
| number (not applicable)     | 16                                                        | 16                                                              | 16                   |  |

### Statistical analyses

|                                         |                                                                                                      |
|-----------------------------------------|------------------------------------------------------------------------------------------------------|
| Statistical analysis title              | Paired t-tests                                                                                       |
| Comparison groups                       | Xaluprine (liquid formulation of 6-mercaptopurine) v Purinethol (tablet version of 6-mercaptopurine) |
| Number of subjects included in analysis | 32                                                                                                   |
| Analysis specification                  | Pre-specified                                                                                        |
| Analysis type                           | non-inferiority                                                                                      |
| P-value                                 | < 0.05                                                                                               |
| Method                                  | t-test, 1-sided                                                                                      |
| Parameter estimate                      | Mean difference (final values)                                                                       |
| Confidence interval                     |                                                                                                      |
| sides                                   | 2-sided                                                                                              |
| lower limit                             | 0.8                                                                                                  |
| upper limit                             | 1.25                                                                                                 |

| <div>Variability estimate</div> | <div>Standard error of the mean</div> |
|---------------------------------|---------------------------------------|
|---------------------------------|---------------------------------------|

## Adverse events

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

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Timeframe for reporting adverse events:

Upon leaving the trial unit.

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

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### Dictionary used

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

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|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

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Frequency threshold for reporting non-serious adverse events: 0.01 %

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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: As this was a small study, with only 17 participants and a short timeframe, no non-serious adverse events were reported.

## 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

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32519032>