



## Clinical trial results:

**Open label, multi-centre, parallel group study to compare the pharmacokinetics (PK), pharmacodynamics (PD) and safety of febuxostat between pediatric patients ( $\geq 6 < 18$  years of age) and adults.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-001445-61 |
| Trial protocol           | IT HU ES BG    |
| Global end of trial date | 25 July 2018   |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 14 February 2019 |
| First version publication date | 14 February 2019 |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | FLO-02 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03605212 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Menarini Ricerche S.p.A.  |
| Sponsor organisation address | Via Sette Santi 1, Florence, Italy, 50131   |
| Public contact               | Corporate Director of Clinical Sciences, Menarini Ricerche S.p.A., +39 055 56809990, ACapriati@menarini-ricerche.it |
| Scientific contact           | Corporate Director of Clinical Sciences, Menarini Ricerche S.p.A., +39 055 56809990, ACapriati@menarini-ricerche.it |

Notes:

### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-001417-PIP01-12 |
| 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? | Yes                 |

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 25 July 2018 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 25 July 2018 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 25 July 2018 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

-To assess the pharmacokinetics (PK) of febuxostat in pediatric patients ( $\geq 6 < 18$  years of age) and in adults suffering from hematological malignancies at intermediate to high risk of Tumor Lysis Syndrome.  
-To compare the febuxostat exposure in pediatric patients ( $\geq 6 < 18$  years of age) with the one achieved in adults administered with a dose of 120 mg/QD.

Protection of trial subjects:

If any event(s) related to the conduct of the study or the development of the IMP affected the safety of the study participants, the Sponsor and the Investigator were to take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/IECs were to be informed forthwith about these new events and the measures taken.

For patients participating in the study, Menarini Ricerche S.p.A. had stipulated an insurance policy in accordance with local regulatory requirements.

Background therapy:

First cycle of cytotoxic chemotherapy for the treatment of the underlying disease (hematological malignancy) starting 2 days after start of study drug treatment.

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 27 February 2017 |
| 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 | Hungary: 8 |
| Country: Number of subjects enrolled | Spain: 11  |
| Country: Number of subjects enrolled | Italy: 11  |
| Worldwide total number of subjects   | 30         |
| EEA total number of subjects         | 30         |

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)                    | 3  |
| Adolescents (12-17 years)                | 3  |
| Adults (18-64 years)                     | 14 |
| From 65 to 84 years                      | 10 |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The first patient was screened and enrolled on 27 Feb 2017. The last patient completed the study on 16 Jul 2018. The study was conducted at 17 sites in 4 European countries.

### Pre-assignment

Screening details:

A total of 31 patients was screened, of whom 30 were enrolled and 28 completed the study regularly. Two enrolled patients were withdrawn from study drug treatment.

### Period 1

|                              |                |
|------------------------------|----------------|
| Period 1 title               | Day 1          |
| Is this the baseline period? | Yes            |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

Blinding implementation details:

The study was performed according to an open design; no blinding technique was adopted.

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | Cohort 1_Cohort 2_Children |
|------------------|----------------------------|

Arm description:

Children: DAY 1 before first febuxostat dosing.

|  |                            |
|--|----------------------------|
| Arm type                               | Cohort 1_Cohort 2_Children |
| Investigational medicinal product name | not applicable             |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Tablet                     |
| Routes of administration               | Oral use                   |

Dosage and administration details:

Not applicable for baseline period.

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Cohort 3_Cohort 4_Adolescents |
|------------------|-------------------------------|

Arm description:

Adolescents: DAY 1 before first febuxostat dosing.

|  |                               |
|--|-------------------------------|
| Arm type                               | Cohort 3_Cohort 4_Adolescents |
| Investigational medicinal product name | not applicable                |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Tablet                        |
| Routes of administration               | Oral use                      |

Dosage and administration details:

Not applicable for baseline period.

|                  |        |
|------------------|--------|
| <b>Arm title</b> | Adults |
|------------------|--------|

Arm description:

Adults: DAY 1 before first febuxostat dosing.

|          |        |
|----------|--------|
| Arm type | Adults |
|----------|--------|

|  |                |
|--|----------------|
| Investigational medicinal product name | not applicable |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Tablet         |
| Routes of administration               | Oral use       |
| Dosage and administration details:     |                |
| Not applicable for baseline period.    |                |

| Number of subjects in period 1 | Cohort 1_Cohort 2_Children | Cohort 3_Cohort 4_Adolescents | Adults |
|--------------------------------|----------------------------|-------------------------------|--------|
| Started                        | 3                          | 3                             | 24     |
| Completed                      | 3                          | 3                             | 24     |

## Period 2

|                              |                  |
|------------------------------|------------------|
| Period 2 title               | Treatment Period |
| Is this the baseline period? | No               |
| Allocation method            | Not applicable   |
| Blinding used                | Not blinded      |

Blinding implementation details:

The study was performed according to an open design; no blinding technique was adopted.

## Arms

|                              |                            |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes                        |
| Arm title                    | Cohort 1_Cohort 2_Children |

Arm description:

Children (aged  $\geq 6$  -  $< 12$ ).

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Febuxostat 40 mg |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

Cohort 1: 2x20 mg QD.

Minimum treatment duration was for 7 days starting from Visit 1 (Day 1), which should have occurred 2 days prior to the planned start of first chemotherapy cycle. The Investigator was given the possibility to prolong the treatment duration up to 9 days on the basis of the chemotherapy regimen administered to the patient.

|  |                  |
|--|------------------|
| Investigational medicinal product name | Febuxostat 60 mg |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

Cohort 2: 3x20 mg QD.

Minimum treatment duration was for 7 days starting from Visit 1 (Day 1), which should have occurred 2 days prior to the planned start of first chemotherapy cycle. The Investigator was given the possibility to prolong the treatment duration up to 9 days on the basis of the chemotherapy regimen administered to the patient.

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Cohort 3_Cohort 4_Adolescents |
|------------------|-------------------------------|

Arm description:

Adolescents (aged  $\geq 12$  -  $< 18$ ).

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Febuxostat 80 mg |
| Investigational medicinal product code |                  |
| Other name                             | ADENURIC® 80 mg  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

Cohort 3: 1x80 mg QD.

Minimum treatment duration was for 7 days starting from Visit 1 (Day 1), which should have occurred 2 days prior to the planned start of first chemotherapy cycle. The Investigator was given the possibility to prolong the treatment duration up to 9 days on the basis of the chemotherapy regimen administered to the patient.

|  |                   |
|--|-------------------|
| Investigational medicinal product name | Febuxostat 120 mg |
| Investigational medicinal product code |                   |
| Other name                             | ADENURIC® 120 mg  |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Cohort 4: 1x120mg QD.

Minimum treatment duration was for 7 days starting from Visit 1 (Day 1), which should have occurred 2 days prior to the planned start of first chemotherapy cycle. The Investigator was given the possibility to prolong the treatment duration up to 9 days on the basis of the chemotherapy regimen administered to the patient.

|                  |        |
|------------------|--------|
| <b>Arm title</b> | Adults |
|------------------|--------|

Arm description:

Adults

|  |                   |
|--|-------------------|
| Arm type                               | Experimental      |
| Investigational medicinal product name | Febuxostat 120 mg |
| Investigational medicinal product code |                   |
| Other name                             | ADENURIC® 120 mg  |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

1x120 mg QD.

Minimum treatment duration was for 7 days starting from Visit 1 (Day 1), which should have occurred 2 days prior to the planned start of first chemotherapy cycle. The Investigator was given the possibility to prolong the treatment duration up to 9 days on the basis of the chemotherapy regimen administered to the patient.

| <b>Number of subjects in period 2</b> | Cohort 1_Cohort<br>2_Children | Cohort 3_Cohort<br>4_Adolescents | Adults |
|---------------------------------------|-------------------------------|----------------------------------|--------|
| Started                               | 3                             | 3                                | 24     |
| Completed                             | 2                             | 3                                | 23     |
| Not completed                         | 1                             | 0                                | 1      |
| Physician decision                    | -                             | -                                | 1      |
| Adverse event, non-fatal              | 1                             | -                                | -      |

## Baseline characteristics

### Reporting groups

|  |                               |
|--|-------------------------------|
| Reporting group title  | Cohort 1_Cohort 2_Children    |
| Reporting group description:<br>Children: DAY 1 before first febuxostat dosing.    |                               |
| Reporting group title  | Cohort 3_Cohort 4_Adolescents |
| Reporting group description:<br>Adolescents: DAY 1 before first febuxostat dosing. |                               |
| Reporting group title  | Adults                        |
| Reporting group description:<br>Adults: DAY 1 before first febuxostat dosing.      |                               |

| Reporting group values                | Cohort 1_Cohort 2_Children | Cohort 3_Cohort 4_Adolescents | Adults   |
|---------------------------------------|----------------------------|-------------------------------|----------|
| Number of subjects                    | 3                          | 3                             | 24       |
| Age categorical<br>Units: Subjects    |                            |                               |          |
| Children (2-11 years)                 | 3                          | 0                             | 0        |
| Adolescents (12-17 years)             | 0                          | 3                             | 0        |
| Adults (18-64 years)                  | 0                          | 0                             | 14       |
| From 65-84 years                      | 0                          | 0                             | 10       |
| Age continuous<br>Units: years        |                            |                               |          |
| arithmetic mean                       | 7.33                       | 14.00                         | 60.21    |
| standard deviation                    | ± 1.528                    | ± 1.000                       | ± 15.376 |
| Gender categorical<br>Units: Subjects |                            |                               |          |
| Female                                | 1                          | 2                             | 11       |
| Male                                  | 2                          | 1                             | 13       |
| Ethnicity<br>Units: Subjects          |                            |                               |          |
| Hispanic or Latino                    | 0                          | 1                             | 0        |
| Not Hispanic or Latino                | 3                          | 2                             | 24       |
| Race<br>Units: Subjects               |                            |                               |          |
| White                                 | 3                          | 2                             | 23       |
| other                                 | 0                          | 1                             | 1        |
| Weight<br>Units: kg                   |                            |                               |          |
| arithmetic mean                       | 26.13                      | 60.47                         | 75.60    |
| standard deviation                    | ± 2.043                    | ± 19.747                      | ± 15.469 |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 30    |  |  |
| Age categorical<br>Units: Subjects |       |  |  |
| Children (2-11 years)              | 3     |  |  |
| Adolescents (12-17 years)          | 3     |  |  |



|                        |    |  |  |
|------------------------|----|--|--|
| Adults (18-64 years)   | 14 |  |  |
| From 65-84 years       | 10 |  |  |
|                        |    |  |  |
| Age continuous         |    |  |  |
| Units: years           |    |  |  |
| arithmetic mean        |    |  |  |
| standard deviation     | -  |  |  |
| Gender categorical     |    |  |  |
| Units: Subjects        |    |  |  |
| Female                 | 14 |  |  |
| Male                   | 16 |  |  |
| Ethnicity              |    |  |  |
| Units: Subjects        |    |  |  |
| Hispanic or Latino     | 1  |  |  |
| Not Hispanic or Latino | 29 |  |  |
| Race                   |    |  |  |
| Units: Subjects        |    |  |  |
| White                  | 28 |  |  |
| other                  | 2  |  |  |
| Weight                 |    |  |  |
| Units: kg              |    |  |  |
| arithmetic mean        |    |  |  |
| standard deviation     | -  |  |  |

## End points

### End points reporting groups

|  |                               |
|--|-------------------------------|
| Reporting group title  | Cohort 1_Cohort 2_Children    |
| Reporting group description:<br>Children: DAY 1 before first febuxostat dosing.    |                               |
| Reporting group title  | Cohort 3_Cohort 4_Adolescents |
| Reporting group description:<br>Adolescents: DAY 1 before first febuxostat dosing. |                               |
| Reporting group title  | Adults                        |
| Reporting group description:<br>Adults: DAY 1 before first febuxostat dosing.      |                               |
| Reporting group title  | Cohort 1_Cohort 2_Children    |
| Reporting group description:<br>Children (aged $\geq 6$ - $<12$ ).                 |                               |
| Reporting group title  | Cohort 3_Cohort 4_Adolescents |
| Reporting group description:<br>Adolescents (aged $\geq 12$ - $<18$ ).             |                               |
| Reporting group title  | Adults                        |
| Reporting group description:<br>Adults   |                               |

### Primary: Pharmacokinetic parameter: CL/F

|                                   |  |
|-----------------------------------|--|
| End point title                   | Pharmacokinetic parameter: CL/F <sup>[1]</sup> |
| End point description:            |  |
| End point type                    | Primary  |
| End point timeframe:<br>At Day 8. |  |

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: Due to the paucity of data in the minor patient population and in agreement with EMA, there was no statistical analysis. All safety data available were presented until the date of Last Patient Last Visit.

| End point values                     | Cohort 1_Cohort 2_Children | Cohort 3_Cohort 4_Adolescents | Adults           |  |
|--------------------------------------|----------------------------|-------------------------------|------------------|--|
| Subject group type                   | Reporting group            | Reporting group               | Reporting group  |  |
| Number of subjects analysed          | 0 <sup>[2]</sup>           | 0 <sup>[3]</sup>              | 0 <sup>[4]</sup> |  |
| Units: volume/time                   |                            |                               |                  |  |
| arithmetic mean (standard deviation) | ()                         | ()                            | ()               |  |

Notes:

[2] - This study was prematurely terminated. No statistical analyses have been performed.

[3] - This study was prematurely terminated. No statistical analyses have been performed.

[4] - This study was prematurely terminated. No statistical analyses have been performed.

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected during Screening, i.e. after ICF signature until DAY 1, Visit 1 before first IMP intake and specifically Treatment Emergent Signs and Symptoms (TESSs) occurring from first IMP intake at Visit 1, DAY 1 until Visit 10, DAY 14.

Adverse event reporting additional description:

The safety analysis was run on the safety population (all patients who had received at least one dose of study drug). Safety variables included TESS, namely any reported AE occurred or worsened after first study drug intake or any clinically relevant change in safety laboratory parameters, physical examination, PS, 12-Lead ECG and vital signs.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 19.1   |

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Cohort 1 (40mg) |
|-----------------------|-----------------|

Reporting group description:

Cohort 1, Children ( $\geq 6$  -  $<12$ ) receiving 40 mg febuxostat (2 tablets á 20 mg)

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Cohort 3 (80mg) |
|-----------------------|-----------------|

Reporting group description:

Cohort 3, Adolescents ( $\geq 12$  -  $<18$ ) receiving 80 mg febuxostat (1 tablet Adenuric® 80 mg)

|                       |                |
|-----------------------|----------------|
| Reporting group title | Adults (120mg) |
|-----------------------|----------------|

Reporting group description:

Adults ( $\geq 18$ ) receiving 120 mg febuxostat (1 tablet Adenuric® 120 mg)

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

Reporting group description:

Overall

| Serious adverse events                            | Cohort 1 (40mg) | Cohort 3 (80mg) | Adults (120mg)  |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events |                 |                 |                 |
| subjects affected / exposed                       | 1 / 3 (33.33%)  | 0 / 3 (0.00%)   | 5 / 24 (20.83%) |
| number of deaths (all causes)                     | 1               | 0               | 0               |
| number of deaths resulting from adverse events    | 0               | 0               | 0               |
| Investigations                                    |                 |                 |                 |
| Enterobacter test positive                        |                 |                 |                 |
| subjects affected / exposed                       | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   | 1 / 24 (4.17%)  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders              |                 |                 |                 |
| Febrile neutropenia                               |                 |                 |                 |

|  |                |               |                |
|--|----------------|---------------|----------------|
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| General disorders and administration site conditions |                |               |                |
| Mucosal inflammation                                 |                |               |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Gastrointestinal disorders                           |                |               |                |
| Abdominal pain                                       |                |               |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Proctitis  |                |               |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Infections and infestations                          |                |               |                |
| Septic shock   |                |               |                |
| subjects affected / exposed                          | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0         | 0 / 0          |
| Staphylococcal infection                             |                |               |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |

|   |                 |  |  |
|---|-----------------|--|--|
| <b>Serious adverse events</b>                     | Overall         |  |  |
| Total subjects affected by serious adverse events |                 |  |  |
| subjects affected / exposed                       | 6 / 30 (20.00%) |  |  |
| number of deaths (all causes)                     | 1               |  |  |
| number of deaths resulting from adverse events    | 0               |  |  |
| Investigations                                    |                 |  |  |
| Enterobacter test positive                        |                 |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Blood and lymphatic system disorders                 |                |  |  |
| Febrile neutropenia                                  |                |  |  |
| subjects affected / exposed                          | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Mucosal inflammation                                 |                |  |  |
| subjects affected / exposed                          | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Gastrointestinal disorders                           |                |  |  |
| Abdominal pain                                       |                |  |  |
| subjects affected / exposed                          | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Proctitis  |                |  |  |
| subjects affected / exposed                          | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Infections and infestations                          |                |  |  |
| Septic shock   |                |  |  |
| subjects affected / exposed                          | 2 / 30 (6.67%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 1          |  |  |
| Staphylococcal infection                             |                |  |  |
| subjects affected / exposed                          | 1 / 30 (3.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                           | Cohort 1 (40mg) | Cohort 3 (80mg) | Adults (120mg)   |
|---|-----------------|-----------------|------------------|
| Total subjects affected by non-serious adverse events       |                 |                 |                  |
| subjects affected / exposed                                 | 3 / 3 (100.00%) | 3 / 3 (100.00%) | 20 / 24 (83.33%) |
| <b>Vascular disorders</b>                                   |                 |                 |                  |
| Hot flush   |                 |                 |                  |
| subjects affected / exposed                                 | 0 / 3 (0.00%)   | 1 / 3 (33.33%)  | 0 / 24 (0.00%)   |
| occurrences (all)   | 0               | 1               | 0                |
| Hypotension   |                 |                 |                  |
| subjects affected / exposed                                 | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   | 1 / 24 (4.17%)   |
| occurrences (all)   | 0               | 0               | 1                |
| Thrombophlebitis  |                 |                 |                  |
| subjects affected / exposed                                 | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   | 1 / 24 (4.17%)   |
| occurrences (all)   | 0               | 0               | 1                |
| <b>General disorders and administration site conditions</b> |                 |                 |                  |
| Asthenia  |                 |                 |                  |
| subjects affected / exposed                                 | 1 / 3 (33.33%)  | 1 / 3 (33.33%)  | 0 / 24 (0.00%)   |
| occurrences (all)   | 1               | 1               | 0                |
| Chest pain  |                 |                 |                  |
| subjects affected / exposed                                 | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   | 1 / 24 (4.17%)   |
| occurrences (all)   | 0               | 0               | 1                |
| Facial pain   |                 |                 |                  |
| subjects affected / exposed                                 | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   | 1 / 24 (4.17%)   |
| occurrences (all)   | 0               | 0               | 1                |
| Inflammation  |                 |                 |                  |
| subjects affected / exposed                                 | 1 / 3 (33.33%)  | 0 / 3 (0.00%)   | 0 / 24 (0.00%)   |
| occurrences (all)   | 1               | 0               | 0                |
| Malaise   |                 |                 |                  |
| subjects affected / exposed                                 | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   | 1 / 24 (4.17%)   |
| occurrences (all)   | 0               | 0               | 1                |
| Mucosal inflammation  |                 |                 |                  |
| subjects affected / exposed                                 | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   | 2 / 24 (8.33%)   |
| occurrences (all)   | 0               | 0               | 2                |
| Oedema peripheral   |                 |                 |                  |
| subjects affected / exposed                                 | 1 / 3 (33.33%)  | 0 / 3 (0.00%)   | 0 / 24 (0.00%)   |
| occurrences (all)   | 1               | 0               | 0                |
| Pain  |                 |                 |                  |

|   |                     |                     |                      |
|---|---------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                  | 1 / 3 (33.33%)<br>1 | 1 / 3 (33.33%)<br>1 | 0 / 24 (0.00%)<br>0  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)       | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  | 3 / 24 (12.50%)<br>3 |
| Respiratory, thoracic and mediastinal disorders                   |                     |                     |                      |
| Bronchospasm<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 24 (0.00%)<br>0  |
| Cough<br>subjects affected / exposed<br>occurrences (all)         | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 1 / 24 (4.17%)<br>1  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)     | 2 / 3 (66.67%)<br>3 | 0 / 3 (0.00%)<br>0  | 1 / 24 (4.17%)<br>1  |
| Hiccups<br>subjects affected / exposed<br>occurrences (all)       | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 1 / 24 (4.17%)<br>1  |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)      | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 1 / 24 (4.17%)<br>1  |
| Psychiatric disorders   |                     |                     |                      |
| Depression<br>subjects affected / exposed<br>occurrences (all)    | 0 / 3 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 24 (0.00%)<br>0  |
| Hallucination<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 1 / 24 (4.17%)<br>1  |
| Investigations  |                     |                     |                      |
| ALT increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 24 (0.00%)<br>0  |
| AST increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 24 (0.00%)<br>0  |
| BP increased  |                     |                     |                      |



|  |                     |                     |                      |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 1 / 24 (4.17%)<br>1  |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)          | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 24 (0.00%)<br>0  |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)    | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 24 (0.00%)<br>0  |
| Hemoglobin decreased<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 3 (33.33%)<br>2 | 0 / 3 (0.00%)<br>0  | 0 / 24 (0.00%)<br>0  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)             | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 24 (0.00%)<br>0  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)               | 1 / 3 (33.33%)<br>2 | 0 / 3 (0.00%)<br>0  | 0 / 24 (0.00%)<br>0  |
| White blood cell (WBC) count decreased<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | 1 / 3 (33.33%)<br>1 | 2 / 24 (8.33%)<br>2  |
| Cardiac disorders  |                     |                     |                      |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 24 (0.00%)<br>0  |
| Extrasystoles<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 1 / 24 (4.17%)<br>1  |
| Nervous system disorders   |                     |                     |                      |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 3 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 24 (0.00%)<br>0  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 3 (33.33%)<br>1 | 1 / 3 (33.33%)<br>2 | 4 / 24 (16.67%)<br>4 |
| Language disorder  |                     |                     |                      |

|                                      |                |               |                 |
|--------------------------------------|----------------|---------------|-----------------|
| subjects affected / exposed          | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 24 (0.00%)  |
| occurrences (all)                    | 1              | 0             | 0               |
| Paraesthesia                         |                |               |                 |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) | 1 / 24 (4.17%)  |
| occurrences (all)                    | 0              | 0             | 1               |
| Blood and lymphatic system disorders |                |               |                 |
| Anaemia                              |                |               |                 |
| subjects affected / exposed          | 2 / 3 (66.67%) | 0 / 3 (0.00%) | 4 / 24 (16.67%) |
| occurrences (all)                    | 2              | 0             | 4               |
| Lymphopenia                          |                |               |                 |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) | 1 / 24 (4.17%)  |
| occurrences (all)                    | 0              | 0             | 1               |
| Neutropenia                          |                |               |                 |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) | 3 / 24 (12.50%) |
| occurrences (all)                    | 0              | 0             | 3               |
| Thrombocytopenia                     |                |               |                 |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) | 2 / 24 (8.33%)  |
| occurrences (all)                    | 0              | 0             | 2               |
| Gastrointestinal disorders           |                |               |                 |
| Abdominal pain                       |                |               |                 |
| subjects affected / exposed          | 2 / 3 (66.67%) | 0 / 3 (0.00%) | 4 / 24 (16.67%) |
| occurrences (all)                    | 2              | 0             | 4               |
| Abdominal pain upper                 |                |               |                 |
| subjects affected / exposed          | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 24 (0.00%)  |
| occurrences (all)                    | 2              | 0             | 0               |
| Abdominal rigidity                   |                |               |                 |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) | 1 / 24 (4.17%)  |
| occurrences (all)                    | 0              | 0             | 1               |
| Anorectal discomfort                 |                |               |                 |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) | 1 / 24 (4.17%)  |
| occurrences (all)                    | 0              | 0             | 1               |
| Aphthous ulcer                       |                |               |                 |
| subjects affected / exposed          | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 24 (0.00%)  |
| occurrences (all)                    | 1              | 0             | 0               |
| Constipation                         |                |               |                 |

|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed            | 1 / 3 (33.33%) | 3 / 3 (100.00%) | 4 / 24 (16.67%) |
| occurrences (all)                      | 1              | 3               | 5               |
| Diarrhoea                              |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 3 (0.00%)   | 4 / 24 (16.67%) |
| occurrences (all)                      | 0              | 0               | 5               |
| Dyspepsia                              |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 3 (0.00%)   | 1 / 24 (4.17%)  |
| occurrences (all)                      | 0              | 0               | 1               |
| Faeces soft                            |                |                 |                 |
| subjects affected / exposed            | 1 / 3 (33.33%) | 0 / 3 (0.00%)   | 0 / 24 (0.00%)  |
| occurrences (all)                      | 1              | 0               | 0               |
| Gingival swelling                      |                |                 |                 |
| subjects affected / exposed            | 1 / 3 (33.33%) | 0 / 3 (0.00%)   | 0 / 24 (0.00%)  |
| occurrences (all)                      | 1              | 0               | 0               |
| Hematemesis                            |                |                 |                 |
| subjects affected / exposed            | 1 / 3 (33.33%) | 0 / 3 (0.00%)   | 0 / 24 (0.00%)  |
| occurrences (all)                      | 1              | 0               | 0               |
| Hematochezia                           |                |                 |                 |
| subjects affected / exposed            | 1 / 3 (33.33%) | 0 / 3 (0.00%)   | 0 / 24 (0.00%)  |
| occurrences (all)                      | 1              | 0               | 0               |
| Lip pain                               |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 3 (0.00%)   | 1 / 24 (4.17%)  |
| occurrences (all)                      | 0              | 0               | 1               |
| Nausea                                 |                |                 |                 |
| subjects affected / exposed            | 1 / 3 (33.33%) | 1 / 3 (33.33%)  | 0 / 24 (0.00%)  |
| occurrences (all)                      | 1              | 1               | 0               |
| Vomiting                               |                |                 |                 |
| subjects affected / exposed            | 2 / 3 (66.67%) | 0 / 3 (0.00%)   | 2 / 24 (8.33%)  |
| occurrences (all)                      | 4              | 0               | 2               |
| Skin and subcutaneous tissue disorders |                |                 |                 |
| Cold sweat                             |                |                 |                 |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 3 (0.00%)   | 1 / 24 (4.17%)  |
| occurrences (all)                      | 0              | 0               | 1               |
| Erythema                               |                |                 |                 |
| subjects affected / exposed            | 1 / 3 (33.33%) | 0 / 3 (0.00%)   | 0 / 24 (0.00%)  |
| occurrences (all)                      | 1              | 0               | 0               |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Rash  |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 3 (33.33%) | 0 / 24 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Skin discolouration                             |                |                |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 0 / 3 (0.00%)  | 0 / 24 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 3 (33.33%) | 2 / 24 (8.33%) |
| occurrences (all)                               | 0              | 1              | 2              |
| Limb discomfort                                 |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  | 1 / 24 (4.17%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Musculoskeletal pain                            |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 3 (33.33%) | 0 / 24 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Pain in extremity                               |                |                |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 0 / 3 (0.00%)  | 0 / 24 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Temporomandibular joint syndrome                |                |                |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 0 / 24 (0.00%) |
| occurrences (all)                               | 1              | 1              | 0              |
| Infections and infestations                     |                |                |                |
| Oral herpes                                     |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 3 (33.33%) | 0 / 24 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Metabolism and nutrition disorders              |                |                |                |
| Decreased appetite                              |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  | 1 / 24 (4.17%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Fluid retention                                 |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  | 2 / 24 (8.33%) |
| occurrences (all)                               | 0              | 0              | 2              |
| Hyperglycaemia                                  |                |                |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 1 / 24 (4.17%) |
| occurrences (all)                               | 1              | 2              | 1              |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Hyperkalaemia               |                |                |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%)  | 0 / 24 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Hyperphosphataemia          |                |                |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 3 (33.33%) | 0 / 24 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Hypo HDL cholesterolaemia   |                |                |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%)  | 0 / 24 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Hypocalcaemia               |                |                |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%)  | 1 / 24 (4.17%) |
| occurrences (all)           | 1              | 0              | 1              |
| Hypokalaemia                |                |                |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  | 1 / 24 (4.17%) |
| occurrences (all)           | 0              | 0              | 1              |

| <b>Non-serious adverse events</b>                     | Overall          |  |  |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 26 / 30 (86.67%) |  |  |
| Vascular disorders                                    |                  |  |  |
| Hot flush   |                  |  |  |
| subjects affected / exposed                           | 1 / 30 (3.33%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Hypotension   |                  |  |  |
| subjects affected / exposed                           | 1 / 30 (3.33%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Thrombophlebitis                                      |                  |  |  |
| subjects affected / exposed                           | 1 / 30 (3.33%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| General disorders and administration site conditions  |                  |  |  |
| Asthenia  |                  |  |  |
| subjects affected / exposed                           | 2 / 30 (6.67%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| Chest pain  |                  |  |  |
| subjects affected / exposed                           | 1 / 30 (3.33%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Facial pain   |                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 30 (3.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Inflammation                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Malaise   |                 |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Mucosal inflammation                            |                 |  |  |
| subjects affected / exposed                     | 2 / 30 (6.67%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| Oedema peripheral                               |                 |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Pain  |                 |  |  |
| subjects affected / exposed                     | 2 / 30 (6.67%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| Pyrexia   |                 |  |  |
| subjects affected / exposed                     | 4 / 30 (13.33%) |  |  |
| occurrences (all)                               | 4               |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Bronchospasm                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Cough   |                 |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Epistaxis                                       |                 |  |  |
| subjects affected / exposed                     | 3 / 30 (10.00%) |  |  |
| occurrences (all)                               | 4               |  |  |
| Hiccups   |                 |  |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Wheezing  |                 |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1 |  |  |
| Psychiatric disorders                            |                     |  |  |
| Depression                                       |                     |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1 |  |  |
| Hallucination                                    |                     |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1 |  |  |
| Investigations                                   |                     |  |  |
| ALT increased                                    |                     |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1 |  |  |
| AST increased                                    |                     |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1 |  |  |
| BP increased                                     |                     |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1 |  |  |
| Blood triglycerides increased                    |                     |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1 |  |  |
| Gamma-glutamyltransferase increased              |                     |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1 |  |  |
| Hemoglobin decreased                             |                     |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>2 |  |  |
| Neutrophil count decreased                       |                     |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1 |  |  |
| Platelet count decreased                         |                     |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>2 |  |  |
| White blood cell (WBC) count decreased           |                     |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 4 / 30 (13.33%)<br>4 |  |  |
| Cardiac disorders                                |                      |  |  |
| Arrhythmia                                       |                      |  |  |
| subjects affected / exposed                      | 1 / 30 (3.33%)       |  |  |
| occurrences (all)                                | 1                    |  |  |
| Extrasystoles                                    |                      |  |  |
| subjects affected / exposed                      | 1 / 30 (3.33%)       |  |  |
| occurrences (all)                                | 1                    |  |  |
| Nervous system disorders                         |                      |  |  |
| Dizziness  |                      |  |  |
| subjects affected / exposed                      | 1 / 30 (3.33%)       |  |  |
| occurrences (all)                                | 1                    |  |  |
| Headache   |                      |  |  |
| subjects affected / exposed                      | 6 / 30 (20.00%)      |  |  |
| occurrences (all)                                | 7                    |  |  |
| Language disorder                                |                      |  |  |
| subjects affected / exposed                      | 1 / 30 (3.33%)       |  |  |
| occurrences (all)                                | 1                    |  |  |
| Paraesthesia                                     |                      |  |  |
| subjects affected / exposed                      | 1 / 30 (3.33%)       |  |  |
| occurrences (all)                                | 1                    |  |  |
| Blood and lymphatic system disorders             |                      |  |  |
| Anaemia  |                      |  |  |
| subjects affected / exposed                      | 6 / 30 (20.00%)      |  |  |
| occurrences (all)                                | 6                    |  |  |
| Lymphopenia                                      |                      |  |  |
| subjects affected / exposed                      | 1 / 30 (3.33%)       |  |  |
| occurrences (all)                                | 1                    |  |  |
| Neutropenia                                      |                      |  |  |
| subjects affected / exposed                      | 3 / 30 (10.00%)      |  |  |
| occurrences (all)                                | 3                    |  |  |
| Thrombocytopenia                                 |                      |  |  |
| subjects affected / exposed                      | 2 / 30 (6.67%)       |  |  |
| occurrences (all)                                | 2                    |  |  |
| Gastrointestinal disorders                       |                      |  |  |



|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| Abdominal pain              |                 |  |  |
| subjects affected / exposed | 6 / 30 (20.00%) |  |  |
| occurrences (all)           | 6               |  |  |
| Abdominal pain upper        |                 |  |  |
| subjects affected / exposed | 1 / 30 (3.33%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Abdominal rigidity          |                 |  |  |
| subjects affected / exposed | 1 / 30 (3.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Anorectal discomfort        |                 |  |  |
| subjects affected / exposed | 1 / 30 (3.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Aphthous ulcer              |                 |  |  |
| subjects affected / exposed | 1 / 30 (3.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Constipation                |                 |  |  |
| subjects affected / exposed | 8 / 30 (26.67%) |  |  |
| occurrences (all)           | 9               |  |  |
| Diarrhoea                   |                 |  |  |
| subjects affected / exposed | 4 / 30 (13.33%) |  |  |
| occurrences (all)           | 5               |  |  |
| Dyspepsia                   |                 |  |  |
| subjects affected / exposed | 1 / 30 (3.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Faeces soft                 |                 |  |  |
| subjects affected / exposed | 1 / 30 (3.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Gingival swelling           |                 |  |  |
| subjects affected / exposed | 1 / 30 (3.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hematemesis                 |                 |  |  |
| subjects affected / exposed | 1 / 30 (3.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hematochezia                |                 |  |  |
| subjects affected / exposed | 1 / 30 (3.33%)  |  |  |
| occurrences (all)           | 1               |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Lip pain<br>subjects affected / exposed<br>occurrences (all)             | 1 / 30 (3.33%)<br>1  |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 2 / 30 (6.67%)<br>2  |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 4 / 30 (13.33%)<br>6 |  |  |
| Skin and subcutaneous tissue disorders                                   |                      |  |  |
| Cold sweat<br>subjects affected / exposed<br>occurrences (all)           | 1 / 30 (3.33%)<br>1  |  |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)             | 1 / 30 (3.33%)<br>1  |  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 30 (3.33%)<br>1  |  |  |
| Skin discolouration<br>subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1  |  |  |
| Musculoskeletal and connective tissue disorders                          |                      |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 3 / 30 (10.00%)<br>3 |  |  |
| Limb discomfort<br>subjects affected / exposed<br>occurrences (all)      | 1 / 30 (3.33%)<br>1  |  |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1  |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)    | 1 / 30 (3.33%)<br>1  |  |  |
| Temporomandibular joint syndrome   |                      |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 2 / 30 (6.67%)<br>2  |  |  |
| Infections and infestations<br>Oral herpes<br>subjects affected / exposed<br>occurrences (all)               | 1 / 30 (3.33%)<br>1  |  |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1  |  |  |
| Fluid retention<br>subjects affected / exposed<br>occurrences (all)  | 2 / 30 (6.67%)<br>2  |  |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)   | 4 / 30 (13.33%)<br>4 |  |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1  |  |  |
| Hyperphosphataemia<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 30 (3.33%)<br>1  |  |  |
| Hypo HDL cholesterolaemia<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 30 (3.33%)<br>1  |  |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 30 (6.67%)<br>2  |  |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 30 (3.33%)<br>1  |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 02 February 2017 | Besides others, clarification that UA analyses in blood sample safety tests could be done in both specimen, serum or plasma, with the same normal reference ranges.  |
| 03 February 2017 | Country specific Protocol Amendment for Hungary clarifying that the exclusion or withdrawal of adult and pediatric patients with severe renal dysfunction will be based on the cut off of the CLcr < 30 mL/min and < 60 mL/min/1.73 m <sup>2</sup> , respectively. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Per EMA waiver, the Sponsor early stopped the study on 25July2018 because febuxostat was of no benefit in TLS prevention in minors over existing treatments. Adverse Events are reported, primary endpoint data are not reported due to paucity of data.

Notes: