



## Clinical trial results:

### Pharmacokinetic study of the opioid ketobemidone in children and adolescents after intravenous administration

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2006-006717-32 |
| Trial protocol           | SE             |
| Global end of trial date | 03 June 2008   |

#### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)                                 |
| This version publication date     | 21 May 2021                                  |
| First version publication date    | 21 May 2021                                  |
| Summary attachment (see zip file) | Published article 2009 (AAS2009fulltext.pdf) |

#### Trial information

##### Trial identification

|                       |     |
|-----------------------|-----|
| Sponsor protocol code | 554 |
|-----------------------|-----|

##### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | -   |
| ClinicalTrials.gov id (NCT number) | -   |
| WHO universal trial number (UTN)   | -   |
| Other trial identifiers            | Ethics committee Karolinska Institutet Stockholm : 2007/4:1 |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Stockholms Läns Landsting  |
| Sponsor organisation address | Karolinska University Hospital, Stockholm, Sweden, 17176   |
| Public contact               | Stefan Lundeborg, Karolinska University Hospital, +46 851777189, stefan.lundeborg@sll.se                 |
| Scientific contact           | Pediatric Pain treatment Service, Karolinska University Hospital, +46 851770000, stefan.lundeborg@sll.se |

Notes:

#### Paediatric regulatory details

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

Notes:

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**Results analysis stage**

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 03 June 2008  |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 30 April 2008 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 03 June 2008  |
| Was the trial ended prematurely?                     | No            |

Notes:

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**General information about the trial**

Main objective of the trial:

Determination of elimination half life of ketobemidone after intravenous injection in children

Protection of trial subjects:

Postoperative pain management following standard protocol at the hospital. The study drug was part of the pain treatment.

Background therapy:

Standard analgesic treatment with paracetamol, clonidine and opioids as needed.

Evidence for comparator:

Not applicable

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 10 September 2007 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Sweden: 30 |
| Worldwide total number of subjects   | 30         |
| EEA total number of subjects         | 30         |

Notes:

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**Subjects enrolled per age group**

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 5  |
| Infants and toddlers (28 days-23 months)  | 15 |
| Children (2-11 years)                     | 10 |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

30 children who underwent a planned surgical procedure and in need of postoperative opioid treatment.

### Pre-assignment

Screening details:

31 children were screened and 30 participated and consent was given.

### Period 1

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

Blinding implementation details:

Not applicable

### Arms

|           |              |
|-----------|--------------|
| Arm title | Ketobemidone |
|-----------|--------------|

Arm description:

Study drug used for all enrolled patients

|  |                            |
|--|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | Ketobemidone hydrochloride |
| Investigational medicinal product code | N02AB01                    |
| Other name                             |                            |
| Pharmaceutical forms                   | Injection                  |
| Routes of administration               | Intravenous bolus use      |

Dosage and administration details:

0.05 mg/kg for neonates and up to 3 months of age, 0.1 mg/kg over the age of 3 months.

|                                       |              |
|---------------------------------------|--------------|
| <b>Number of subjects in period 1</b> | Ketobemidone |
| Started                               | 30           |
| Completed                             | 30           |

## Baseline characteristics

### Reporting groups

|   |               |
|---|---------------|
| Reporting group title   | Overall trial |
| Reporting group description:                                  |               |
| Three groups: neonates up to 90 days; 1-2.5 years; 7-10 years |               |

| Reporting group values  | Overall trial | Total |  |
|---|---------------|-------|--|
| Number of subjects  | 30            | 30    |  |
| Age categorical   |               |       |  |
| Units: Subjects   |               |       |  |
| In utero  | 0             | 0     |  |
| Preterm newborn infants (gestational age < 37 wks)                                      | 0             | 0     |  |
| Newborns (0-27 days)  | 5             | 5     |  |
| Infants and toddlers (28 days-23 months)  | 15            | 15    |  |
| Children (2-11 years)   | 10            | 10    |  |
| Adolescents (12-17 years)   | 0             | 0     |  |
| Adults (18-64 years)  | 0             | 0     |  |
| From 65-84 years  | 0             | 0     |  |
| 85 years and over   | 0             | 0     |  |
| Age continuous  |               |       |  |
| Children neonates to 3 months (group A) 1 to 2.5 years (groupB) and 7-10 years (groupC) |               |       |  |
| Units: years  |               |       |  |
| median  | 2.5           |       |  |
| full range (min-max)  | 0 to 11       | -     |  |
| Gender categorical  |               |       |  |
| Units: Subjects   |               |       |  |
| Female  | 13            | 13    |  |
| Male  | 17            | 17    |  |
| Children  |               |       |  |
| Children aged 0-11 years  |               |       |  |
| Units: Subjects   |               |       |  |
| Age   | 30            | 30    |  |
| Children  |               |       |  |
| Children divided in 3 groups  |               |       |  |
| Units: Age  |               |       |  |
| median  | 2.5           |       |  |
| full range (min-max)  | 0 to 11       | -     |  |

### Subject analysis sets

|   |                                   |
|---|-----------------------------------|
| Subject analysis set title  | Ketobemidone plasma concentration |
| Subject analysis set type   | Full analysis                     |
| Subject analysis set description:   |                                   |
| Plasma concentration of ketobemidone were analysed. Blood sampling was performed at 6 occasions after bolus dose was given. |                                   |
| Subject analysis set title  | Ketobemidone comparison group     |
| Subject analysis set type   | Sub-group analysis                |

| <b>Reporting group values</b>   | Ketobemidone plasma concentration | Ketobemidone comparison group |  |
|---|-----------------------------------|-------------------------------|--|
| Number of subjects  | 30                                | 24                            |  |
| Age categorical   |                                   |                               |  |
| Units: Subjects   |                                   |                               |  |
| In utero  | 0                                 |                               |  |
| Preterm newborn infants (gestational age < 37 wks)                                      | 0                                 |                               |  |
| Newborns (0-27 days)  | 5                                 |                               |  |
| Infants and toddlers (28 days-23 months)  | 15                                |                               |  |
| Children (2-11 years)   | 10                                |                               |  |
| Adolescents (12-17 years)   | 0                                 |                               |  |
| Adults (18-64 years)  | 0                                 |                               |  |
| From 65-84 years  | 0                                 |                               |  |
| 85 years and over   | 0                                 |                               |  |
| Age continuous  |                                   |                               |  |
| Children neonates to 3 months (group A) 1 to 2.5 years (groupB) and 7-10 years (groupC) |                                   |                               |  |
| Units: years  |                                   |                               |  |
| median  | 27                                |                               |  |
| full range (min-max)  | 5 to 35                           |                               |  |
| Gender categorical  |                                   |                               |  |
| Units: Subjects   |                                   |                               |  |
| Female  | 15                                |                               |  |
| Male  | 9                                 |                               |  |
| Children  |                                   |                               |  |
| Children aged 0-11 years  |                                   |                               |  |
| Units: Subjects   |                                   |                               |  |
| Age   | 30                                |                               |  |
| Children  |                                   |                               |  |
| Children divided in 3 groups  |                                   |                               |  |
| Units: Age  |                                   |                               |  |
| median  | 2.5                               |                               |  |
| full range (min-max)  | 0 to 11                           |                               |  |

## End points

### End points reporting groups

|   |                                   |
|---|-----------------------------------|
| Reporting group title   | Ketobemidone                      |
| Reporting group description:  |                                   |
| Study drug used for all enrolled patients   |                                   |
| Subject analysis set title  | Ketobemidone plasma concentration |
| Subject analysis set type   | Full analysis                     |
| Subject analysis set description:   |                                   |
| Plasma concentration of ketobemidone were analysed. Blood sampling was performed at 6 occasions after bolus dose was given. |                                   |
| Subject analysis set title  | Ketobemidone comparison group     |
| Subject analysis set type   | Sub-group analysis                |
| Subject analysis set description:   |                                   |
| Age groups as described   |                                   |

### Primary: Pharmacokinetic parameter

|                              |                           |
|------------------------------|---------------------------|
| End point title              | Pharmacokinetic parameter |
| End point description:       |                           |
| Last patient enrolled        |                           |
| End point type               | Primary                   |
| End point timeframe:         |                           |
| September 2007 to April 2008 |                           |

| End point values            | Ketobemidone plasma concentration | Ketobemidone comparison group |  |  |
|-----------------------------|-----------------------------------|-------------------------------|--|--|
| Subject group type          | Subject analysis set              | Subject analysis set          |  |  |
| Number of subjects analysed | 24                                | 24                            |  |  |
| Units: ng/ml                |                                   |                               |  |  |
| number (not applicable)     | 24                                | 24                            |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | AUC   |
| Statistical analysis description:       |   |
| AUC /mg/kg in relation to age groups    |   |
| Comparison groups                       | Ketobemidone comparison group v Ketobemidone plasma concentration |
| Number of subjects included in analysis | 48  |
| Analysis specification                  | Post-hoc  |
| Analysis type                           | other <sup>[1]</sup>  |
| P-value                                 | ≤ 0.05  |
| Method                                  | Spearman Rank Correlation   |

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Notes:

[1] - comparison between age groups

## Adverse events

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

Timeframe for reporting adverse events:

From time of administration of bolus dose of ketobemidone and up to 72 hours post injection.

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

### Dictionary used

|                 |              |
|-----------------|--------------|
| Dictionary name | CRF protocol |
|-----------------|--------------|

|                    |   |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Ketobemidone |
|-----------------------|--------------|

Reporting group description:

Children administered a bolus dose of ketobemidone

| Serious adverse events                            | Ketobemidone   |  |  |
|---|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 0 / 30 (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                            | Ketobemidone   |  |  |
|---|----------------|--|--|
| Total subjects affected by non-serious adverse events |                |  |  |
| subjects affected / exposed                           | 0 / 30 (0.00%) |  |  |

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: Nausea was registered in 2 patients but this might have been caused by several factors as the surgical procedure, the anesthesia as well as the post operative analgesics including ketobemidone or other given opioids



## 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

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

|   |
|---|
| Nausea as a non serious side effects could be explained by many factors including the use of ketobemidone, surgical procedure and anesthesia. |
|---|

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/19839946>