



## Clinical trial results:

### An Open-Label, Randomised, Active Controlled, Multi-Centre Phase 3 Study to Evaluate the Safety and Efficacy of Danaparoid vs Argatroban in Treatment of Subjects with Acute HIT (HITSOVA study)

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2018-002473-21       |
| Trial protocol           | DE FR CZ PL ES HR IT |
| Global end of trial date | 10 June 2022         |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 27 May 2023  |
| First version publication date | 27 May 2023  |

#### Trial information

##### Trial identification

|                       |                     |
|-----------------------|---------------------|
| Sponsor protocol code | ERGCR-18-ORGHIT-001 |
|-----------------------|---------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03809481 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Aspen Global Incorporated   |
| Sponsor organisation address | GBS Plaza, Cur La Salette et Royal Roads,, Grand Bay, Mauritius,                  |
| Public contact               | Michelle Singleton, Aspen Pharmacare Holdings Limited, MSingleton@aspenpharma.com |
| Scientific contact           | Michelle Singleton, Aspen Pharmacare Holdings Limited, MSingleton@aspenpharma.com |

Notes:

##### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 04 February 2020 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 04 February 2020 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 10 June 2022     |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

To show that for the treatment of subjects with acute heparin-induced thrombocytopenia (HIT) danaparoid use is not inferior to argatroban in terms of efficacy.

Protection of trial subjects:

due to the serious condition the subjects are under intensive care in the hospital

Background therapy:

All subjects will start a VKA after the platelet count has normalized to a stable plateau for 2 consecutive days, with at least 5 days overlap of receiving study drug, unless contraindicated, and continue taking a VKA until Day 42 in case of HIT without thrombosis and at the Investigator's discretion in case of HIT with thrombosis but at least for 3 months.

Evidence for comparator:

The comparator, argatroban, is approved to treat HIT in several countries and was found to be safe and well-tolerated in this population.

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 01 March 2019 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                           |
|--------------------------------------|---------------------------|
| Country: Number of subjects enrolled | Germany: 1                |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 3 |
| Country: Number of subjects enrolled | Serbia: 3                 |
| Worldwide total number of subjects   | 7                         |
| EEA total number of subjects         | 1                         |

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)                     | 0 |

|                           |   |
|---------------------------|---|
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years)      | 5 |
| From 65 to 84 years       | 2 |
| 85 years and over         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Subject screening occurred in Italy, Germany, Serbia, and Bosnia Herzegovina in the period from July 2019 up to early March 2020 after that COVID resulted in a recruitment halt.

### Pre-assignment

Screening details:

in total 14 subjects were screened. 7 screenfailed. One of the main reason for failing screening was a negative HIT test.

### Period 1

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

Blinding implementation details:

Not applicable not blinded

### Arms

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

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

Arm description:

Subjects received danaparoid sodium, a therapeutic infusion for at least 7 days (target plasma anti-factor Xa activity 0.4 to 0.8 units/mL) after which it was continued in preparation for the transition to Vitamin K antagonist (VKA).

|  |                                 |
|--|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | danaparoid sodium               |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Infusion                        |

Dosage and administration details:

Intravenous (IV) loading bolus injection of 2250 U (i.e. 3 ampoules) (for subjects less than 55 kg 1500 U, if over 90 kg, 3750 U) immediately followed by  
2 step-down IV infusions at 400 U/h for 4 hours, followed by 300 U/h for 4 hours, and then the maintenance infusion of 200 U/h until the Day 14 (or longer if needed).

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

Arm description:

Subjects received argatroban, a therapeutic infusion for up to 14 days. Intravenous therapy was stopped in the period between 7 and 14 days.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Active comparator                     |
| Investigational medicinal product name | argatroban monohydrate                |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

The initial dosage of argatroban in adult subjects without hepatic impairment in HIT was 2 microgram/kg/min, administered as a continuous infusion. Before argatroban was administered, heparin therapy was to be discontinued and a baseline aPTT value obtained  
Subjects received argatroban, a therapeutic infusion for up to 14 days. Intravenous therapy was stopped in the period between 7 and 14 days.

| <b>Number of subjects in period 1</b> | danaparoid | argatroban |
|---------------------------------------|------------|------------|
| Started                               | 4          | 3          |
| Completed                             | 2          | 0          |
| Not completed                         | 2          | 3          |
| Adverse event, non-fatal              | 1          | 1          |
| Death                                 | 1          | 1          |
| confirmed as non HIT                  | -          | 1          |

## Baseline characteristics

### Reporting groups

|  |               |
|--|---------------|
| Reporting group title  | overall trial |
| Reporting group description:   |               |
| Of the 7 subjects randomized, 5 subjects (71.43%) were female, and 2 subjects (28.57%) were male. Majority of subjects (6/7) were not Hispanic or Latino. All the subjects 7/7 (100.0%) were white. Most of the subjects (57.14%) had Intensive care unit (ICU) admission. |               |
| Overall, the median age of subjects was 59.0 years (range: 48-79 years), with median age 58.0 years (range: 50-79 years) for danaparoid group and 61.0 years (range: 48-78 years) for argatroban group.  |               |
| Overall the median weight was 74.50 kg (range: 59.0106.0 kg).  |               |

| Reporting group values  | overall trial | Total |  |
|---|---------------|-------|--|
| Number of subjects  | 7             | 7     |  |
| Age categorical   |               |       |  |
| Overall, the median age of subjects was 59.0 years (range: 48-79 years), with median age 58.0 years (range: 50-79 years) for danaparoid group and 61.0 years (range: 48-78 years) for argatroban group. |               |       |  |
| Units: Subjects   |               |       |  |
| In utero  | 0             | 0     |  |
| Preterm newborn infants (gestational age < 37 wks)  | 0             | 0     |  |
| Newborns (0-27 days)  | 0             | 0     |  |
| Infants and toddlers (28 days-23 months)  | 0             | 0     |  |
| Children (2-11 years)   | 0             | 0     |  |
| Adolescents (12-17 years)   | 0             | 0     |  |
| Adults (18-64 years)  | 5             | 5     |  |
| From 65-84 years  | 2             | 2     |  |
| 85 years and over   | 0             | 0     |  |
| Age continuous  |               |       |  |
| Overall, the median age of subjects was 59.0 years (range: 48-79 years), with median age 58.0 years (range: 50-79 years) for danaparoid group and 61.0 years (range: 48-78 years) for argatroban group. |               |       |  |
| Units: years  |               |       |  |
| median  | 59            |       |  |
| full range (min-max)  | 48 to 79      | -     |  |
| Gender categorical  |               |       |  |
| Of the 7 subjects randomized, 5 subjects (71.43%) were female, and 2 subjects (28.57%) were male.   |               |       |  |
| Units: Subjects   |               |       |  |
| Female  | 5             | 5     |  |
| Male  | 2             | 2     |  |

### Subject analysis sets

|                                   |              |
|-----------------------------------|--------------|
| Subject analysis set title        | Efficacy     |
| Subject analysis set type         | Per protocol |
| Subject analysis set description: |              |
| all randomized subjects           |              |

|   |          |  |  |
|---|----------|--|--|
| <b>Reporting group values</b>   | Efficacy |  |  |
| Number of subjects  | 7        |  |  |
| Age categorical   |          |  |  |
| Overall, the median age of subjects was 59.0 years (range: 48-79 years), with median age 58.0 years (range: 50-79 years) for danaparoid group and 61.0 years (range: 48-78 years) for argatroban group. |          |  |  |
| Units: Subjects   |          |  |  |
| In utero  | 0        |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks)   | 0        |  |  |
| Newborns (0-27 days)  | 0        |  |  |
| Infants and toddlers (28 days-23 months)  | 0        |  |  |
| Children (2-11 years)   | 0        |  |  |
| Adolescents (12-17 years)   | 0        |  |  |
| Adults (18-64 years)  | 5        |  |  |
| From 65-84 years  | 2        |  |  |
| 85 years and over   | 0        |  |  |
| Age continuous  |          |  |  |
| Overall, the median age of subjects was 59.0 years (range: 48-79 years), with median age 58.0 years (range: 50-79 years) for danaparoid group and 61.0 years (range: 48-78 years) for argatroban group. |          |  |  |
| Units: years  |          |  |  |
| median  |          |  |  |
| full range (min-max)  |          |  |  |
| Gender categorical  |          |  |  |
| Of the 7 subjects randomized, 5 subjects (71.43%) were female, and 2 subjects (28.57%) were male.   |          |  |  |
| Units: Subjects   |          |  |  |
| Female  |          |  |  |
| Male  |          |  |  |

## End points

### End points reporting groups

|   |              |
|---|--------------|
| Reporting group title   | danaparoid   |
| Reporting group description:<br>Subjects received danaparoid sodium, a therapeutic infusion for at least 7 days (target plasma anti-factor Xa activity 0.4 to 0.8 units/mL) after which it was continued in preparation for the transition to Vitamin K antagonist (VKA). |              |
| Reporting group title   | argatroban   |
| Reporting group description:<br>Subjects received argatroban, a therapeutic infusion for up to 14 days. Intravenous therapy was stopped in the period between 7 and 14 days.  |              |
| Subject analysis set title  | Efficacy     |
| Subject analysis set type   | Per protocol |
| Subject analysis set description:<br>all randomized subjects  |              |

### Primary: efficacy

|  |                         |
|--|-------------------------|
| End point title  | efficacy <sup>[1]</sup> |
| End point description:<br>Primary Endpoint<br>The proportion of treatment responders at Day 44, was to be defined as those subjects who had not experienced any of the following events: <ul style="list-style-type: none"><li>• New or extended venous and/or arterial thrombosis, including gangrene/skin necrosis,</li><li>• All-cause mortality,</li><li>• Unplanned amputation, including ischaemic gut resection, were the primary endpoint for the comparison of efficacy between the treatment groups.</li></ul> |                         |
| End point type   | Primary                 |
| End point timeframe:<br>The primary efficacy endpoint (composite endpoint) is defined as treatment response at Day 44.   |                         |
| Notes:<br>[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.<br>Justification: due to the limit number of patients no statistical analysis was performed.   |                         |

| End point values            | danaparoid       | argatroban       | Efficacy             |  |
|-----------------------------|------------------|------------------|----------------------|--|
| Subject group type          | Reporting group  | Reporting group  | Subject analysis set |  |
| Number of subjects analysed | 0 <sup>[2]</sup> | 0 <sup>[3]</sup> | 0 <sup>[4]</sup>     |  |
| Units: events               |                  |                  |                      |  |
| number (not applicable)     |                  |                  |                      |  |

Notes:  
[2] - No efficacy analysis was performed due to low number of subjects  
[3] - no efficacy analysis was performed due to low number of subjects  
[4] - No analysis performed due to low number of subjects

### Statistical analyses

No statistical analyses for this end point

### Secondary: efficacy and safety

|                 |                     |
|-----------------|---------------------|
| End point title | efficacy and safety |
|-----------------|---------------------|



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End point description:

Secondary Endpoints

The following endpoints were planned to be assessed to further evaluate the safety and efficacy of the two treatments:

- Percentage of subjects with consistent increases in platelets at Days 3, 5, and 7 (to identify early response) defined as monotonically increasing platelet counts, measured two days apart on days 3 ( $\pm 1$  day), 5 ( $\pm 1$  day) and 7 ( $\pm 1$  day).
- Deaths due to TE or bleeding up until Day 44
- Incidence of fatal or non-fatal major bleeding up until Day 44
- New or extended thrombosis, including gangrene/skin necrosis
- Unplanned amputation, including ischaemic gut resect
- All-cause mortality

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

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End point timeframe:

up until Day 44

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| End point values            | danaparoid       | argatroban       |  |  |
|-----------------------------|------------------|------------------|--|--|
| Subject group type          | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed | 0 <sup>[5]</sup> | 0 <sup>[6]</sup> |  |  |
| Units: events               |                  |                  |  |  |
| number (not applicable)     |                  |                  |  |  |

Notes:

[5] - due to the low number of subjects no statistical analysis was performed

[6] - due to the low number of subjects no statistical analysis was performed

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs were reported at start of IMP administration upto day 44 of the follow up period.

Adverse event reporting additional description:

To describe the safety of danaparoid in comparison to argatroban

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 22     |

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | danaparoid |
|-----------------------|------------|

Reporting group description:

Subjects received danaparoid sodium, a therapeutic infusion for at least 7 days (target plasma anti-factor Xa activity 0.4 to 0.8 units/mL) after which it was continued in preparation for the transition to Vitamin K antagonist (VKA).

|                       |            |
|-----------------------|------------|
| Reporting group title | argatroban |
|-----------------------|------------|

Reporting group description:

Subjects received argatroban, a therapeutic infusion for up to 14 days. Intravenous therapy was stopped in the period between 7 and 14 days.

| Serious adverse events  | danaparoid     | argatroban     |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events                   |                |                |  |
| subjects affected / exposed   | 2 / 4 (50.00%) | 2 / 3 (66.67%) |  |
| number of deaths (all causes)                                       | 2              | 2              |  |
| number of deaths resulting from adverse events                      | 0              | 0              |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |  |
| Malignant neoplasm progression                                      |                |                |  |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Cardiac disorders   |                |                |  |
| Intracardiac thrombus   |                |                |  |
| subjects affected / exposed   | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Infections and infestations   |                |                |  |
| Septic shock  |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sepsis  |                |                |  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | danaparoid     | argatroban     |  |
|---|----------------|----------------|--|
| Total subjects affected by non-serious adverse events |                |                |  |
| subjects affected / exposed                           | 3 / 4 (75.00%) | 2 / 3 (66.67%) |  |
| Investigations  |                |                |  |
| Activated partial thromboplastin time prolonged       |                |                |  |
| subjects affected / exposed                           | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |  |
| occurrences (all)                                     | 0              | 1              |  |
| Vascular disorders                                    |                |                |  |
| Hypertension  |                |                |  |
| subjects affected / exposed                           | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                                     | 1              | 0              |  |
| General disorders and administration site conditions  |                |                |  |
| Peripheral swelling                                   |                |                |  |
| subjects affected / exposed                           | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |  |
| occurrences (all)                                     | 0              | 1              |  |
| Gastrointestinal disorders                            |                |                |  |
| Haemorrhoids  |                |                |  |
| subjects affected / exposed                           | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                                     | 1              | 0              |  |
| Infections and infestations                           |                |                |  |
| Urinary tract infection                               |                |                |  |
| subjects affected / exposed                           | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                                     | 1              | 0              |  |
| Gangrene  |                |                |  |

|                             |               |                |  |
|-----------------------------|---------------|----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 3 (33.33%) |  |
| occurrences (all)           | 0             | 1              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 18 January 2019   | protocol version 6; <ul style="list-style-type: none"><li>• Update of study design with Schedule of events, population, inclusion and exclusion criteria, number of subjects per treatment arm to suffice to reject the 1-sided null hypothesis.</li><li>• IMP was updated with the information that use of VKA should be delayed until substantial resolution thrombocytopenia (e.g., platelets &gt; 100 × 10<sup>9</sup>/L) to avoid coumarin associated with microvascular thrombosis and venous limb gangrene.</li><li>• Adjudication Committee was added to Independent Data Monitoring Committee.</li></ul>  |
| 10 September 2019 | protocol version 7; <ul style="list-style-type: none"><li>• Update of study population by adding definition of Acute systemic reaction when heparin infusion was given, and specification that Pediatric subjects will not be included in every country in this study. The countries that allow inclusion of Pediatric patients are France, USA, Italy and Russia.</li><li>• Update inclusion and exclusion criteria, and concomitant medications (Women of child-bearing age who are taking VKA should use effective contraception until one month after cessation of use).</li><li>• IMP dosage was updated: <a href="https://www.medicines.ie/medicines/orgaran-750-anti-xa-units-0-6ml-solution-for-injection-33247/">https://www.medicines.ie/medicines/orgaran-750-anti-xa-units-0-6ml-solution-for-injection-33247/</a>. In cases of impaired renal function (i.e. eGFR&lt;30 mL/min/1.73m<sup>2</sup>) the maintenance dose should be reduced to 150 U/h. For further maintenance dose modifications.</li><li>• If the subject has sustained an accidental traumatic bleed (falling out of bed etc.) then danaparoid should be transiently discontinued until the bleeding has stopped and the maintenance infusion restarted without a loading dose when it is considered safe to do so.</li><li>• Thromboembolism section updated.</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date          | Interruption  | Restart date |
|---------------|---|--------------|
| 01 April 2020 | The study was stopped in April 2020 because of the COVID-19 pandemic. In June 2022 it was decided to close the study as due to low recruitment before the pandemic and the remaining effects of the pandemic making it difficult to complete the study. | -            |

Notes:

### Limitations and caveats

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

The efficacy data are not reported in this CSR as the study was stopped in April 2020 as a result of the COVID-19 pandemic and due to the low number of subjects, no efficacy results can be concluded in this clinical trial.

Notes: