



Clinical trial results:

Phase II, single centre, double blinded, cross-over dose confirmation study using two morphine-naloxone i.v. solutions

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-005903-34 |
| Trial protocol | AT |
| Global end of trial date | 02 August 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 18 April 2022 |
| First version publication date | 18 April 2022 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | KKSMUW2011-09 |
|-----------------------|---------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | G.L. Pharma GmbH |
| Sponsor organisation address | Schlossplatz 1, Lannach, Austria, 8502 |
| Public contact | G. L. Pharma GmbH, G. L. Pharma GmbH, +43 3136825770, office@gl-pharma.at |
| Scientific contact | G. L. Pharma GmbH, G. L. Pharma GmbH, +43 3136825770, office@gl-pharma.at |

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 | 16 January 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 January 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 August 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the appropriate ratio of morphine and naloxone to suppress the pleasurable effects of intravenous morphine and precipitate withdrawal reactions.

Protection of trial subjects:

health monitoring personnel, rescue medication, measurements of vital signs

Background therapy:

diagnosis of opioid dependence currently undergoing morphine maintenance treatment

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 09 January 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Austria: 56 |
| Worldwide total number of subjects | 56 |
| EEA total number of subjects | 56 |

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) | 56 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

2013 - 2015, Austria

Pre-assignment

Screening details:

vital signs, complete blood count, medical history, inclusion/exclusion criteria,

Pre-assignment period milestones

| | |
|--|-------------------|
| Number of subjects started | 56 |
| Intermediate milestone: Number of subjects | oral morphine: 44 |
| Number of subjects completed | 44 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Screening failure: 10 |
| Reason: Number of subjects | Consent withdrawn by subject: 2 |

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Morphine i.v. |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|--|-----------------|
| Arm title | Morphine i.v. |
| Arm description: - | |
| Arm type | Baseline |
| Investigational medicinal product name | Morphine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

individual doses

| | |
|---|---------------|
| Number of subjects in period 1^[1] | Morphine i.v. |
| Started | 44 |
| Completed | 43 |
| Not completed | 1 |
| Consent withdrawn by subject | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A number of 56 subjects were enrolled for screening. There were 10 screening failures, and 2 subjects withdraw their consent. Finally, 44 subjects started the baseline period.

Period 2

| | |
|------------------------------|---|
| Period 2 title | Morphine-Naloxone 100:1 vs. Morphine |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Data analyst, Carer, Assessor, Subject |

Arms

| | |
|------------------------------|------------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | Morphine-Naloxone ratio 100:1 i.v. |

Arm description: -

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | MorphineNaloxone 100:1 Ampoules / Solution for Injection |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

individual doses

| | |
|------------------|----------------|
| Arm title | Morphine Mono1 |
|------------------|----------------|

Arm description: -

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Morphine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

individual doses

| Number of subjects in period 2 | Morphine-Naloxone ratio 100:1 i.v. | Morphine Mono1 |
|---------------------------------------|------------------------------------|----------------|
| Started | 43 | 43 |
| Completed | 43 | 42 |
| Not completed | 0 | 1 |
| Consent withdrawn by subject | - | 1 |

Period 3

| | |
|------------------------------|---|
| Period 3 title | Morphine-Naloxone 200:1 vs. Morphine |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

| | |
|------------------|------------------------------------|
| Arm title | Morphine-Naloxone ratio 200:1 i.v. |
|------------------|------------------------------------|

Arm description: -

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | MorphineNaloxone 200:1 Ampoules / Solution for Injection |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

individual doses

| | |
|------------------|----------------|
| Arm title | Morphine Mono2 |
|------------------|----------------|

Arm description: -

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Morphine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

individual doses

| Number of subjects in period 3 | Morphine-Naloxone ratio 200:1 i.v. | Morphine Mono2 |
|---------------------------------------|------------------------------------|----------------|
| Started | 42 | 42 |
| Completed | 40 | 42 |
| Not completed | 2 | 0 |
| Adverse event, non-fatal | 1 | - |
| Protocol deviation | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Morphine i.v. |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Morphine i.v. | Total | |
|--|---------------|-------|--|
| Number of subjects | 44 | 44 | |
| Age categorical | | | |
| all subjects | | | |
| 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) | 0 | 0 | |
| From 65-84 years | 44 | 44 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 44 | 44 | |

End points

End points reporting groups

| | |
|--------------------------------|------------------------------------|
| Reporting group title | Morphine i.v. |
| Reporting group description: - | |
| Reporting group title | Morphine-Naloxone ratio 100:1 i.v. |
| Reporting group description: - | |
| Reporting group title | Morphine Mono1 |
| Reporting group description: - | |
| Reporting group title | Morphine-Naloxone ratio 200:1 i.v. |
| Reporting group description: - | |
| Reporting group title | Morphine Mono2 |
| Reporting group description: - | |

Primary: AUC(0-20) of SOWS-G

| | |
|------------------------|--|
| End point title | AUC(0-20) of SOWS-G ^[1] |
| End point description: | Signs and symptoms of opiate withdrawal, according to Short Opiate Withdrawal Scale German (SOWSG), AUC of Total Score between 0 and 20 minutes after application of study drug. |
| End point type | Primary |
| End point timeframe: | 0 and 20 minutes after application of study drug |

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: The study was carried out in a cross-over design. No statistical analysis was reported to prevent automated summing up of the arms population.

For the primary endpoint SOWS-G, 42 subjects were included. The analysis was pre-specified, the analysis type was superiority with a p-value of < 0.05. The method used was Wilcoxon (Mann-Whitney).

| End point values | Morphine-Naloxone ratio 100:1 i.v. | Morphine-Naloxone ratio 200:1 i.v. | Morphine Mono1 | Morphine Mono2 |
|-------------------------------------|------------------------------------|------------------------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 42 | 40 | 42 | 40 |
| Units: total score * minutes | | | | |
| geometric mean (standard deviation) | 239 (± 127) | 104 (± 110) | 21 (± 37) | 18 (± 36) |

Statistical analyses

No statistical analyses for this end point

Primary: AUC of Pupil diameter

| | |
|------------------------|---|
| End point title | AUC of Pupil diameter ^[2] |
| End point description: | Pupil diameter, mean of left and right eye, AUC between 0 and 20 minutes after application of study drug. |
| End point type | Primary |

End point timeframe:

0-20 minutes after administration of study drug

Notes:

[2] - 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: The study was carried out in a cross-over design. No statistical analysis was reported to prevent automated summing up of the arms population.

For the primary endpoint pupil diameter, 42 subjects were included. The analysis was pre-specified, the analysis type was superiority with a p-value of < 0.05. The method used was Wilcoxon (Mann-Whitney).

| End point values | Morphine-Naloxone ratio 100:1 i.v. | Morphine-Naloxone ratio 200:1 i.v. | Morphine Mono1 | Morphine Mono2 |
|-------------------------------------|------------------------------------|------------------------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 41 | 40 | 41 | 40 |
| Units: mm * minutes | | | | |
| geometric mean (standard deviation) | 17.1 (± 10.5) | 13.7 (± 11.2) | -10.2 (± 8.2) | -10.6 (± 10.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-20) of OOWS

End point title AUC(0-20) of OOWS

End point description:

Objective Opiate Withdrawal Scale

End point type Secondary

End point timeframe:

0-20 minutes

| End point values | Morphine-Naloxone ratio 100:1 i.v. | Morphine-Naloxone ratio 200:1 i.v. | Morphine Mono1 | Morphine Mono2 |
|-------------------------------------|------------------------------------|------------------------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 42 | 40 | 42 | 40 |
| Units: total score * minutes | | | | |
| geometric mean (standard deviation) | 131 (± 43) | 68 (± 42) | 7 (± 11) | 5 (± 9) |

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-20) of Wang scale

End point title AUC(0-20) of Wang scale

End point description:

Wang Scale (third)

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 0-20 minutes | |

| End point values | Morphine-Naloxone ratio 100:1 i.v. | Morphine-Naloxone ratio 200:1 i.v. | Morphine Mono1 | Morphine Mono2 |
|-------------------------------------|------------------------------------|------------------------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 21 | 23 | 21 |
| Units: total score * minutes | | | | |
| geometric mean (standard deviation) | 253 (± 148) | 67 (± 77) | 2 (± 7) | 1 (± 2) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

full report

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 10 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | all subjects |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events | all subjects | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | all subjects | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 44 (47.73%) | | |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | | |
| occurrences (all) | 2 | | |
| Dysgeusia | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences (all) | 1 | | |
| Coma | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences (all) | 1 | | |
| Injection site erythema | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences (all) | 1 | | |
| Injection site urticaria | | | |
| subjects affected / exposed | 5 / 44 (11.36%) | | |
| occurrences (all) | 7 | | |
| Injection site plaque | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences (all) | 1 | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | | |
| occurrences (all) | 2 | | |
| Flatulence | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | | |
| occurrences (all) | 3 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | | |
| occurrences (all) | 2 | | |
| Enteritis | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | | |
| occurrences (all) | 2 | | |
| Diarrhoea | | | |

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 8 / 44 (18.18%) 9 | | |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | | |
| Cough subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | | |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 3 | | |
| Urticaria subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | | |
| Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | | |
| Infections and infestations Abscess limb subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 26 July 2012 | Change of principal investigator |
| 30 August 2013 | Addition of an additional questionnaire for the subjects |
| 15 April 2014 | Adjustments to safety reporting and informed consent |
| 17 October 2014 | Change of principal investigator |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported