# Clinical trial results:
# An open-label, dose escalation, single-dose administration, multi-center phase I/II trial of FG001 (an imaging agent), in patients with glioblastoma scheduled for neurosurgery

## Summary

| | |
|---|---|
| EudraCT number | 2020-003089-38 |
| Trial protocol | DK SE |
| Global end of trial date | 12 October 2023 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 27 October 2024 |
| First version publication date | 27 October 2024 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | FG001-CT-001 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | FluoGuiode A/s |
| Sponsor organisation address | Ole Maaløes Vej 3, København N, Denmark, 2200 |
| Public contact | Morten Albrechtsen, FluoGuide A/S, ma@fluoguide.com |
| Scientific contact | Morten Albrechtsen, FluoGuide A/S, ma@fluoguide.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 | 10 June 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 July 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 October 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Phase I:
1. To evaluate the safety and tolerability of single i.v. doses of FG001 in patients with malignant glioma scheduled for surgery
2. To establish the optimal dose for imaging of FG001 in patients with malignant glioma

Phase II:
1. To evaluate the efficacy of FG001 in patients with malignant glioma undergoing surgery and to compare it with the efficacy of 5-ALA in patients with malignant glioma undergoing surgery

Protection of trial subjects:

The trial patients were given ample time to consider participation in the trial before the consent was obtained. The informed consent documents were signed and dated by each patient and the Investigator, who had provided the information to the patient regarding the trial, before these patients had been exposed to any trial-related procedures, including screening tests for eligibility.

All patients received a copy of the patient information and the signed ICF. If new information potentially relevant to the trial patient's willingness to continue participation in the trial became available, a new patient information and ICF were provided to the IECs (and regulatory authorities, if required) for review and approval. The trial patients were informed about this new information and new consents were obtained.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 04 November 2020 |
| 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 | Sweden: 5 |
| Country: Number of subjects enrolled | Denmark: 59 |
| Worldwide total number of subjects | 64 |
| EEA total number of subjects | 64 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| wk | |
|---|---|
| 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) | 40 |
| From 65 to 84 years | 24 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

During screening, eligible patients with the suspicion of the primary malignant glioma, as judged by MRI, were included in the trial. Each participant received a unique screening number which was entered in a screening log. At baseline visit an evaluation of their complete medical history, vital signs, etc. was performed.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Phase I |

Arm description:

Phase I was an open-label, non-randomized FiH phase with single-dose administration of FG001. It consisted of the dose escalation and dose elaboration parts, conducted at 1 site in Denmark. 40 patients were treated in Phase I, where all patients received both 5-ALA (as standard of care) and FG001.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FG001 |
| Investigational medicinal product code | |
| Other name | ICG-Glu-Glu-AE05 |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

The Investigational Medicinal Product (IMP) FG001 Drug Product i.v. (FG001 DP) was delivered in vials each vial containing 5.2 mg of freeze-dried FG001 for reconstitution with 5.0 m of sterile water for injection (sWfI) before use. All patients received a single dose of reconstituted IMP through a slow i.v. injection lasting for up to 10 minutes.
In phase I, FG001 was administered i.v. in the morning on the day of the surgery (dose escalation) or in the evening the day before the surgery (dose elaboration).

| | |
|---|---|
| Investigational medicinal product name | 5-ALA |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

A commercially available 5-ALA product for phases I and II (Gliolan® for oral administration) was purchased and supplied by the hospital. 5-ALA was administered in the morning, 2-4 hours before the surgery as an oral solution.

| | |
|---|---|
| **Arm title** | Phase II - 5-ALA |

Arm description:

In Phase II, 24 patients were randomized to FG001 and 5-ALA arms. Randomization was performed after baseline assessments and before any trial treatment administration. 5-ALA served as the active comparator to FG001, where patients were randomized to either FG001 or 5-ALA treatment.

| | |
|---|---|
| Arm type | Active comparator |

| | |
|---|---|
| Investigational medicinal product name | 5-ALA |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

A commercially available 5-ALA product for phases I and II (Gliolan® for oral administration) was purchased and supplied by the hospital. 5-ALA was administered in the morning, 2-4 hours before the surgery as an oral solution.

| **Arm title** | Phase II - FG001 |
|---|---|

Arm description:

In Phase II, 24 patients were randomized to FG001 and 5-ALA arms. Randomization was performed after baseline assessments and before any trial treatment administration. FG001 served as the experimetnal arm in Part II, where patients were randomized to either FG001 or 5-ALA treatment.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FG001 |
| Investigational medicinal product code | |
| Other name | ICG-Glu-Glu-AE05 |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

The Investigational Medicinal Product (IMP) FG001 Drug Product i.v. (FG001 DP) was delivered in vials each vial containing 5.2 mg of freeze-dried FG001 for reconstitution with 5.0 m of sterile water for injection (sWfI) before use. All patients randomized to FG001 received a single dose of reconstituted IMP through a slow i.v. injection lasting for up to 10 minutes.
In phase II, FG001 was administered i.v. in the evening the day before the surgery. Patients received the planned dose of FG001 (36 mg per patient).

| **Number of subjects in period 1** | Phase I | Phase II - 5-ALA | Phase II - FG001 |
|---|---|---|---|
| Started | 40 | 12 | 12 |
| Completed | 40 | 12 | 12 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Phase I |
| Reporting group description: | |
| Phase I was an open-label, non-randomized FiH phase with single-dose administration of FG001. It consisted of the dose escalation and dose elaboration parts, conducted at 1 site in Denmark. 40 patients were treated in Phase I, where all patients received both 5-ALA (as standard of care) and FG001. | |
| Reporting group title | Phase II - 5-ALA |
| Reporting group description: | |
| In Phase II, 24 patients were randomized to FG001 and 5-ALA arms. Randomization was performed after baseline assessments and before any trial treatment administration. 5-ALA served as the active comparator to FG001, where patients were randomized to either FG001 or 5-ALA treatment. | |
| Reporting group title | Phase II - FG001 |
| Reporting group description: | |
| In Phase II, 24 patients were randomized to FG001 and 5-ALA arms. Randomization was performed after baseline assessments and before any trial treatment administration. FG001 served as the experimetnal arm in Part II, where patients were randomized to either FG001 or 5-ALA treatment. | |

| Reporting group values | Phase I | Phase II - 5-ALA | Phase II - FG001 |
|---|---|---|---|
| Number of subjects | 40 | 12 | 12 |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 58.2 | 66.6 | 58.3 |
| standard deviation | ± 10 | ± 6.5 | ± 13.9 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 16 | 4 | 4 |
| Male | 24 | 8 | 8 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 64 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (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) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 24 | | |
| Male | 40 | | |

**Subject analysis sets**

| | |
|---|---|
| Subject analysis set title | Phase I: Escalation - Cohort 1 (1mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FG001: 1 mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 2 (2mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FG001 2mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 3 (4mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FG001 4mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 4 (8mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FG001 8mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 5 (16mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FG001 16 mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 6 (24mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FG001 24 mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 7 (36mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FG001 36 mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 8 (48mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FG001 48 mg | |
| Subject analysis set title | Phase I: Elaboration - Cohort 1 (16mg) |
| Subject analysis set type | Full analysis |

Subject analysis set description:
FG001 16 mg

| | |
|---|---|
| Subject analysis set title | Phase I: Elaboration - Cohort 2 (36mg) |
| Subject analysis set type | Full analysis |

Subject analysis set description:
FG001 36 mg

| | |
|---|---|
| Subject analysis set title | Phase I: Elaboration - Cohort 3 (48mg) |
| Subject analysis set type | Full analysis |

Subject analysis set description:
FG001 48 mg

| **Reporting group values** | Phase I: Escalation - Cohort 1 (1mg) | Phase I: Escalation - Cohort 2 (2mg) | Phase I: Escalation - Cohort 3 (4mg) |
|---|---|---|---|
| Number of subjects | 3 | 3 | 3 |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 66.3 | 60 | 60.3 |
| standard deviation | ± 9.8 | ± 5.1 | ± 8.1 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 3 | 1 | 1 |
| Male | 0 | 3 | 3 |

| **Reporting group values** | Phase I: Escalation - Cohort 4 (8mg) | Phase I: Escalation - Cohort 5 (16mg) | Phase I: Escalation - Cohort 6 (24mg) |
|---|---|---|---|
| Number of subjects | 4 | 3 | 3 |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |

| | | | |
|---|---|---|---|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 57.8 | 49.0 | 60.3 |
| standard deviation | ± 7.5 | ± 5.2 | ± 9.5 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 2 | 1 | 1 |
| Male | 2 | 2 | 2 |

| **Reporting group values** | Phase I: Escalation - Cohort 7 (36mg) | Phase I: Escalation - Cohort 8 (48mg) | Phase I: Elaboration - Cohort 1 (16mg) |
|---|---|---|---|
| Number of subjects | 3 | 4 | 5 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 57.7 | 60.5 | 58.0 |
| standard deviation | ± 13.3 | ± 3.9 | ± 8.5 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1 | 3 | 1 |
| Male | 2 | 1 | 4 |

| **Reporting group values** | Phase I: Elaboration - Cohort 2 (36mg) | Phase I: Elaboration - Cohort 3 (48mg) | |
|---|---|---|---|
| Number of subjects | 5 | 4 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 62.6 | 47.8 | |
| standard deviation | ± 12.4 | ± 10.7 | |

| Gender categorical<br>Units: Subjects | | | |
|---|---|---|---|
| Female | 1 | 1 | |
| Male | 4 | 3 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Phase I |
| Reporting group description: | |
| Phase I was an open-label, non-randomized FiH phase with single-dose administration of FG001. It consisted of the dose escalation and dose elaboration parts, conducted at 1 site in Denmark. 40 patients were treated in Phase I, where all patients received both 5-ALA (as standard of care) and FG001. | |
| Reporting group title | Phase II - 5-ALA |
| Reporting group description: | |
| In Phase II, 24 patients were randomized to FG001 and 5-ALA arms. Randomization was performed after baseline assessments and before any trial treatment administration. 5-ALA served as the active comparator to FG001, where patients were randomized to either FG001 or 5-ALA treatment. | |
| Reporting group title | Phase II - FG001 |
| Reporting group description: | |
| In Phase II, 24 patients were randomized to FG001 and 5-ALA arms. Randomization was performed after baseline assessments and before any trial treatment administration. FG001 served as the experimetnal arm in Part II, where patients were randomized to either FG001 or 5-ALA treatment. | |
| Subject analysis set title | Phase I: Escalation - Cohort 1 (1mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| FG001: 1 mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 2 (2mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| FG001 2mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 3 (4mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| FG001 4mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 4 (8mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| FG001 8mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 5 (16mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| FG001 16 mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 6 (24mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| FG001 24 mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 7 (36mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| FG001 36 mg | |
| Subject analysis set title | Phase I: Escalation - Cohort 8 (48mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| FG001 48 mg | |
| Subject analysis set title | Phase I: Elaboration - Cohort 1 (16mg) |
| Subject analysis set type | Full analysis |

| | |
|---|---|
| Subject analysis set description: FG001 16 mg | |
| Subject analysis set title | Phase I: Elaboration - Cohort 2 (36mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FG001 36 mg | |
| Subject analysis set title | Phase I: Elaboration - Cohort 3 (48mg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FG001 48 mg | |

## Primary: TBR (mean) values obtained with ORBEYE and ZEISS Pentero

| | |
|---|---|
| End point title | TBR (mean) values obtained with ORBEYE and ZEISS Pentero[1] |
| End point description: The trial was descriptive in nature, and no confirmatory hypotheses were tested. TBR = Tumor to Background Ratio. | |
| End point type | Primary |
| End point timeframe: Duration of the Phase I part of the trial. | |

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 trial was descriptive in nature, and no confirmatory hypotheses were tested.

| End point values | Phase I: Escalation - Cohort 5 (16mg) | Phase I: Escalation - Cohort 6 (24mg) | Phase I: Escalation - Cohort 7 (36mg) | Phase I: Escalation - Cohort 8 (48mg) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 3[2] | 3[3] | 3[4] | 2[5] |
| Units: TBR | | | | |
| arithmetic mean (full range (min-max)) | | | | |
| ORBEYE | 1.5 (1.3 to 1.7) | 1.43 (1.2 to 1.7) | 1.53 (1.4 to 1.6) | 1.4 (1.4 to 1.4) |
| ZEISS | 0 (0 to 0) | 2.1 (2.1 to 2.1) | 1.4 (1.4 to 1.4) | 1.6 (1.5 to 1.7) |

Notes:

[2] - n = 3 ORBEYE

[3] - n = 3 ORBEYE, n = 2 ZEISS

[4] - n = 3 ORBEYE, n = 1 ZEISS

[5] - n = 2 ORBEYE, n = 2 ZEISS

| End point values | Phase I: Elaboration - Cohort 1 (16mg) | Phase I: Elaboration - Cohort 2 (36mg) | Phase I: Elaboration - Cohort 3 (48mg) | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4[6] | 4[7] | 4[8] | |
| Units: TBR | | | | |
| arithmetic mean (full range (min-max)) | | | | |
| ORBEYE | 1.5 (1.3 to 1.8) | 1.9 (1.7 to 2.2) | 1.4 (1.3 to 1.5) | |
| ZEISS | 0 (0 to 0) | 2.65 (1.9 to 3.7) | 2.45 (2.2 to 2.8) | |

Notes:

[6] - n = 4 ORBEYE

[7] - n = 4 ORBEYE, n = 4 ZEISS

[8] - n = 4 ORBEYE, n = 4 ZEISS

## Statistical analyses

No statistical analyses for this end point

## Primary: Indeterminated or unexpected fluorescent tissue

| End point title | Indeterminated or unexpected fluorescent tissue[9][10] |
|---|---|

End point description:

This endpoint corresponded to the occurrence of at least 1 indeterminated or unexpected fluorescent tissue, where FG001- or 5-ALA-induced fluorescence was consistent with the histopathological assessment. This endpoint was assessed by calculating the proportion of patients with favorable outcome. The outcome was considered favorable if indeterminated or unexpected fluorescence was observed in the EOS cavity and the subsequent histopathological assessment confirmed that biopsies taken from the fluorescent area of this cavity contained tumor cells.

| End point type | Primary |
|---|---|

End point timeframe:

Duration of Phase II part of trial.

Notes:

[9] - 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 trial was descriptive in nature, and no confirmatory hypotheses were tested.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The results are provided for the sub-groups, where all sub groups belong to Phase I arm.

| **End point values** | Phase II - 5-ALA | Phase II - FG001 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: Patients | 12 | 12 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Entire duration of trial.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Phase I cohorts |
| Reporting group description: - | |
| Reporting group title | Phase II cohorts |

Reporting group description: -

| Serious adverse events | Phase I cohorts | Phase II cohorts | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 40 (17.50%) | 0 / 24 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Extradural haematoma | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 40 (7.50%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Phase I cohorts | Phase II cohorts | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 40 / 40 (100.00%) | 24 / 24 (100.00%) | |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 21 / 40 (52.50%) | 9 / 24 (37.50%) | |
| occurrences (all) | 21 | 9 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 5 / 40 (12.50%) | 0 / 24 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 5 / 40 (12.50%) | 2 / 24 (8.33%) | |
| occurrences (all) | 5 | 2 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 40 (10.00%) | 3 / 24 (12.50%) | |
| occurrences (all) | 4 | 3 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 4 / 24 (16.67%) | |
| occurrences (all) | 1 | 4 | |
| Blood chloride decreased | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 3 / 24 (12.50%) | |
| occurrences (all) | 0 | 3 | |
| PCO2 increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 40 (0.00%) | 3 / 24 (12.50%) | |
| occurrences (all) | 0 | 3 | |
| PO2 increased | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 3 / 24 (12.50%) | |
| occurrences (all) | 0 | 3 | |
| Bilirubin conjugated increased | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 24 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Blood lactic acid increased | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 24 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Injury, poisoning and procedural complications | | | |
| Procedural headache | | | |
| subjects affected / exposed | 19 / 40 (47.50%) | 5 / 24 (20.83%) | |
| occurrences (all) | 19 | 5 | |
| Pneumocephalus | | | |
| subjects affected / exposed | 11 / 40 (27.50%) | 7 / 24 (29.17%) | |
| occurrences (all) | 11 | 7 | |
| Incision site pain | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 11 / 24 (45.83%) | |
| occurrences (all) | 0 | 11 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | 3 / 24 (12.50%) | |
| occurrences (all) | 3 | 3 | |
| Hypotension | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | 1 / 24 (4.17%) | |
| occurrences (all) | 3 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 11 / 40 (27.50%) | 3 / 24 (12.50%) | |
| occurrences (all) | 11 | 3 | |
| Dizziness | | | |
| subjects affected / exposed | 8 / 40 (20.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Hemianopia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 40 (7.50%) | 0 / 24 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | 2 / 24 (8.33%) | |
| occurrences (all) | 3 | 2 | |
| Aphasia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 2 | 1 | |
| Diplopia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Dysaesthesia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Nervous system disorder | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hemianopia homonymous | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 24 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 9 / 40 (22.50%) | 3 / 24 (12.50%) | |
| occurrences (all) | 9 | 3 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 24 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 24 / 40 (60.00%) | 2 / 24 (8.33%) | |
| occurrences (all) | 24 | 2 | |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 40 (15.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Constipation | | | |
| subjects affected / exposed | 5 / 40 (12.50%) | 0 / 24 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Psychiatric disorders | | | |
| Adjustment disorder | | | |
| subjects affected / exposed | 4 / 40 (10.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 2 | 1 | |
| Hallucination, visual | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 2 / 24 (8.33%) | |
| occurrences (all) | 2 | 2 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in jaw | | | |
| subjects affected / exposed | 6 / 40 (15.00%) | 2 / 24 (8.33%) | |
| occurrences (all) | 6 | 2 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 2 / 24 (8.33%) | |
| occurrences (all) | 1 | 2 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 28 / 40 (70.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 28 | 1 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 24 / 40 (60.00%) | 13 / 24 (54.17%) | |
| occurrences (all) | 24 | 13 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 14 / 40 (35.00%) | 12 / 24 (50.00%) | |
| occurrences (all) | 14 | 12 | |
| Hypermagnesaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 13 / 40 (32.50%) | 1 / 24 (4.17%) | |
| occurrences (all) | 13 | 1 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 8 / 40 (20.00%) | 9 / 24 (37.50%) | |
| occurrences (all) | 8 | 9 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 6 / 40 (15.00%) | 4 / 24 (16.67%) | |
| occurrences (all) | 6 | 4 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | 4 / 24 (16.67%) | |
| occurrences (all) | 3 | 4 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 5 / 24 (20.83%) | |
| occurrences (all) | 2 | 5 | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Acidosis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 24 (8.33%) | |
| occurrences (all) | 0 | 2 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 20 August 2020 | Protocol version 2.0, amendment as response to GNA comments from the DKMA. |
| 25 March 2021 | Protocol version 3.0, amendment to include dose elaboration phase. |
| 08 September 2021 | Protocol version 4.0, amendment to include morning administration. |
| 05 August 2022 | Protocol version 5.1, amendment to move into Phase II of the trial. |
| 18 January 2023 | Protocol version 6.0, amendment to change the secondary objective of the trial. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/36416941