



Clinical trial results:

Automated pupillometry and NIRS-EEG to detect signatures of consciousness in acute brain injury after apomorphine and methylphenidate stimulation: A placebo-controlled, randomized, cross-over study

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2021-001453-31 |
| Trial protocol | DK |
| Global end of trial date | 18 November 2023 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 23 October 2025 |
| First version publication date | 23 October 2025 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | CONMED3 |
|-----------------------|---------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Copenhagen University Hospital Rigshospitalet |
| Sponsor organisation address | Inge Lehmanns Vej 8, Copenhagen, Denmark, 2100 |
| Public contact | Department of Neurology, Copenhagen University Hospital Rigshospitalet, 0045 35456368, daniel.kondziella@regionh.dk |
| Scientific contact | Department of Neurology, Copenhagen University Hospital Rigshospitalet, 0045 35456368, daniel.kondziella@regionh.dk |

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 | 09 September 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 November 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 November 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

1. To investigate, in a placebo-controlled, randomized, cross-over setting, the potential effects on pupillary function and neurovascular coupling with administrations of 20 mg methylphenidate in patients with acute disorder of consciousness.
2. To investigate, in a placebo-controlled, randomized cross-over setting, the potential effects on pupillary function and neurovascular coupling with subcutaneous injections of 2 mg apomorphine in patients with acute disorder of consciousness.

Protection of trial subjects:

Subjects' rights, safety and confidentiality were ensured by compliance with GCP and all regulations. Informed consent was obtained prior to any study procedure. Oversight and monitoring were performed, and legal representatives were involved where required.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 12 August 2022 |
| 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 | Denmark: 112 |
| Worldwide total number of subjects | 112 |
| EEA total number of subjects | 112 |

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) | 59 |
| From 65 to 84 years | 53 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

The first subject was enrolled on 12 August 2022, and the last participant's final visit occurred on 18 November 2023.

ICUs were screened daily for consecutive patients eligible for trial participation except for weekends, holidays and other times of leave.

Pre-assignment

Screening details:

Eligible patients: Adult patients (≥ 18 years), fluent in Danish or English language, with severe acute traumatic or non-traumatic brain injury in a state of coma, vegetative state/unresponsive wakefulness syndrome or minimal consciousness state according to FOUR and SECONDS.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Assessor |

Arms

| | |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Intervention (Methylphenidate) |

Arm description:

Subjects received one dose of 20 mg methylphenidate tablet suspended in water and administered via a nasogastric tube and we administered subcutaneous placebo injections 0.4 ml of fluid (saline) from a 1 ml syringe.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Methylphenidat |
| Investigational medicinal product code | 29491 |
| Other name | |
| Pharmaceutical forms | Soluble tablet |
| Routes of administration | Nasogastric use |

Dosage and administration details:

20 mg milligrams via a nasogastric tube.

| | |
|------------------|----------------------------|
| Arm title | Intervention (Apomorphine) |
|------------------|----------------------------|

Arm description:

Subcutaneous injection of 2 mg apomorphine, and 8 ml of fluid with a suspended tablet (saline) from a 10 ml gavage syringe administered via a nasogastric tube.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Apomorfin |
| Investigational medicinal product code | 28426 |
| Other name | |
| Pharmaceutical forms | Injection, Cutaneous solution |
| Routes of administration | Solution for injection , Subcutaneous use |

Dosage and administration details:

2 mg milligram administrated with subcutaneous injections.

| | |
|------------------|------------------|
| Arm title | Placebo (Saline) |
|------------------|------------------|

Arm description:

Saline as placebo, either administered via a nasogastric tube or subcutaneous injections. We administered 0.4 ml of fluid (saline) from a 1 ml syringe as well as 8 ml of fluid with a suspended tablet

(saline) from a 10 ml gavage syringe.

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | Saline |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Soluble tablet, Cutaneous solution, Injection |
| Routes of administration | Nasogastric use , Solution for injection , Subcutaneous use |

Dosage and administration details:

subcutaneous injection of 0.4 ml of normal saline from a 1 ml syringe, and 8 ml of fluid with a suspended normal saline tablet from a 10 ml gavage syringe administered via a nasogastric tube.

| Number of subjects in period 1 | Intervention (Methylphenidate) | Intervention (Apomorphine) | Placebo (Saline) |
|---------------------------------------|-----------------------------------|-------------------------------|------------------|
| Started | 39 | 36 | 37 |
| Completed | 39 | 36 | 37 |

Baseline characteristics

Reporting groups

| | |
|---|--------------------------------|
| Reporting group title | Intervention (Methylphenidate) |
| Reporting group description: | |
| Subjects received one dose of 20 mg methylphenidate tablet suspended in water and administered via a nasogastric tube and we administered subcutaneous placebo injections 0.4 ml of fluid (saline) from a 1 ml syringe. | |
| Reporting group title | Intervention (Apomorphine) |
| Reporting group description: | |
| Subcutaneous injection of 2 mg apomorphine, and 8 ml of fluid with a suspended tablet (saline) from a 10 ml gavage syringe administered via a nasogastric tube. | |
| Reporting group title | Placebo (Saline) |
| Reporting group description: | |
| Saline as placebo, either administered via a nasogastric tube or subcutaneous injections. We administered 0.4 ml of fluid (saline) from a 1 ml syringe as well as 8 ml of fluid with a suspended tablet (saline) from a 10 ml gavage syringe. | |

| Reporting group values | Intervention (Methylphenidate) | Intervention (Apomorphine) | Placebo (Saline) |
|---------------------------------------|--------------------------------|----------------------------|------------------|
| Number of subjects | 39 | 36 | 37 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 22 | 18 | 19 |
| From 65-84 years | 17 | 18 | 18 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 62.2 | 62.5 | 63.8 |
| standard deviation | ± 9.0 | ± 9.3 | ± 9.6 |
| Gender categorical Units: Subjects | | | |
| Female | 6 | 12 | 11 |
| Male | 33 | 24 | 26 |

| Reporting group values | Total | | |
|---------------------------------------|-------|--|--|
| Number of subjects | 112 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 59 | | |
| From 65-84 years | 53 | | |
| 85 years and over | 0 | | |
| Age continuous Units: years | | | |
| arithmetic mean | - | | |
| standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 29 | | |
| Male | 83 | | |

End points

End points reporting groups

| | |
|---|--------------------------------|
| Reporting group title | Intervention (Methylphenidate) |
| Reporting group description: Subjects received one dose of 20 mg methylphenidate tablet suspended in water and administered via a nasogastric tube and we administered subcutaneous placebo injections 0.4 ml of fluid (saline) from a 1 ml syringe. | |
| Reporting group title | Intervention (Apomorphine) |
| Reporting group description: Subcutaneous injection of 2 mg apomorphine, and 8 ml of fluid with a suspended tablet (saline) from a 10 ml gavage syringe administered via a nasogastric tube. | |
| Reporting group title | Placebo (Saline) |
| Reporting group description: Saline as placebo, either administered via a nasogastric tube or subcutaneous injections. We administered 0.4 ml of fluid (saline) from a 1 ml syringe as well as 8 ml of fluid with a suspended tablet (saline) from a 10 ml gavage syringe. | |

Primary: Effects of stimulants on pupillary responses during pupillometry

| | |
|---|---|
| End point title | Effects of stimulants on pupillary responses during |
| End point description: In a GLMM analysis, comparing the effects of apomorphine and methylphenidate across different treatment sessions (moderate and hard mental arithmetic tasks combined), measuring pupillary responses. | |
| End point type | Primary |
| End point timeframe: During a session, collecting data from baseline, and respectively, 15 (T15) and 60 (T60) minutes following drug administration. | |
| Notes: [1] - 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 placebo arm serves as the reference group. Treatment effect estimates (e.g., odds ratios with 95% confidence intervals) compare each active treatment to placebo, which by definition does not have an effect estimate itself. | |

| End point values | Intervention (Methylphenidate) | Intervention (Apomorphine) | | |
|----------------------------------|--------------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 36 | | |
| Units: Pupillary dilations | | | | |
| number (confidence interval 95%) | | | | |
| Baseline | 1.29 (0.89 to 1.86) | 1.35 (0.93 to 1.96) | | |
| T15 | 0.76 (0.45 to 1.28) | 1.21 (0.73 to 2.02) | | |
| T60 | 0.76 (0.46 to 1.26) | 0.75 (0.45 to 1.24) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | GLMM |
| Statistical analysis description: | |
| We utilized Generalized Linear Mixed Models (GLMM) ²⁹ with Adaptive Gauss-Hermite Quadrature (nAGQ = 100) using the lme4 package in R to evaluate the impact of drug interventions on pupillary responses at different time points (T15 and T60) and across active paradigms. The fixed effects considered were drug interventions (apomorphine, methylphenidate, or placebo) and the assessment times (T0–T60). | |
| Comparison groups | Intervention (Methylphenidate) v Intervention (Apomorphine) |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Confidence interval | |
| level | 95 % |

Secondary: Clinical arousal effects of stimulants

| | |
|-----------------|---|
| End point title | Clinical arousal effects of stimulants ^[2] |
|-----------------|---|

End point description:

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

End point timeframe:

Assessed 60 minutes after drug administration

Notes:

[2] - 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 placebo arm serves as the reference group. Treatment effect estimates (e.g., odds ratios with 95% confidence intervals) compare each active treatment to placebo, which by definition does not have an effect estimate itself.

| End point values | Intervention (Methylphenidate) | Intervention (Apomorphine) | | |
|----------------------------------|--------------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 36 | | |
| Units: Improved Arousal | | | | |
| number (confidence interval 95%) | 9.96 (1.36 to 235.8) | 5.04 (0.56 to 120.7) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | GLMM |
| Comparison groups | Intervention (Methylphenidate) v Intervention (Apomorphine) |

| | |
|---|----------------------|
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Confidence interval | |
| level | 95 % |

Secondary: Change toward higher consciousness level categories

| | |
|------------------------|--|
| End point title | Change toward higher consciousness level categories ^[3] |
| End point description: | |

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Assessed 60 minutes following drug administration | |

Notes:

[3] - 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 placebo arm serves as the reference group. Treatment effect estimates (e.g., odds ratios with 95% confidence intervals) compare each active treatment to placebo, which by definition does not have an effect estimate itself.

| End point values | Intervention (Methylphenidate) | Intervention (Apomorphine) | | |
|---|--------------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 36 | | |
| Units: Change in consciousness category | | | | |
| number (confidence interval 95%) | 3.41 (0.34 to 88) | 5.67 (0.63 to 169.46) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | GLMM |
| Comparison groups | Intervention (Methylphenidate) v Intervention (Apomorphine) |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 |
| Method | GLMM |
| Parameter estimate | Odds ratio (OR) |
| Confidence interval | |
| level | 95 % |

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

TAES were monitored until six half-lives of the active substance with the longest plasma half-life (i.e. methylphenidate, 3 h) had passed. Deaths were reported based on ICU survival status and not limited to the period of active study drug administration.

Adverse event reporting additional description:

EPR's were screened for adverse events reporting. The process was also externally controlled by staff from the GCP. We observed no adverse events, serious adverse events or suspected unexpected serious adverse reactions related to the study drugs during treatment sessions.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 25 |
|--------------------|----|

Reporting groups

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|-----------------------|-------|
| Reporting group title | Arm 1 |
|-----------------------|-------|

Reporting group description:

Subjects received one dose of 20 mg methylphenidate tablet suspended in water and administered via a nasogastric tube and we administered subcutaneous placebo injections 0.4 ml of fluid (saline) from a 1 ml syringe.

| | |
|-----------------------|-------|
| Reporting group title | Arm 2 |
|-----------------------|-------|

Reporting group description:

Subcutaneous injection of 2 mg apomorphine, and 8 ml of fluid with a suspended tablet (saline) from a 10 ml gavage syringe administered via a nasogastric tube.

| | |
|-----------------------|-------|
| Reporting group title | Arm 3 |
|-----------------------|-------|

Reporting group description:

Saline as placebo, either administered via a nasogastric tube or subcutaneous injections. We administered 0.4 ml of fluid (saline) from a 1 ml syringe as well as 8 ml of fluid with a suspended tablet (saline) from a 10 ml gavage syringe.

| Serious adverse events | Arm 1 | Arm 2 | Arm 3 |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 36 (0.00%) | 0 / 37 (0.00%) |
| number of deaths (all causes) | 11 | 10 | 9 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Arm 1 | Arm 2 | Arm 3 |
|---|----------------|----------------|----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 36 (0.00%) | 0 / 37 (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: No SAE's were present in our study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 15 December 2022 | <p>Summary of Protocol Amendments</p> <p>a. Revision of Inclusion and Exclusion Criteria: The inclusion and exclusion criteria have been revised to include patients with acute brain injury presenting in coma, unresponsive wakefulness syndrome (UWS), or minimally conscious state (MCS).</p> <p>b. Addition of New Study Sites: Screening and recruitment occur on RH units 6021 and 2143. Additional sites, RH units 4131 and 4141, and the intensive unit at Bispebjerg Hospital (BBH) was added.</p> <p>These amendments are described in Supplementary Protocol Version 2.2, dated 15 December 2022.</p> |

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/40501148>