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

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

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	Summary of Protocol Amendments 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). 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. These amendments are described in Supplementary Protocol Version 2.2, dated 15 December 2022.

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