Clinical trial results:
Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU)

Summary

EudraCT number	2017-003829-15
Trial protocol	DK FI ES IT
Global end of trial date	31 August 2023

Results information

Result version number	v1 (current)
This version publication date	13 November 2024
First version publication date	13 November 2024

Trial information

Trial identification

Sponsor protocol code	AID-ICU

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov: NCT03392376

Notes:

Sponsors

Sponsor organisation name	Zealand University Hospital
Sponsor organisation address	Lykkebækvej 1, Copenhagen, Denmark, 4600
Public contact	Lone Musaeus Poulsen, Department of Anaesthesia and intensive Care Medicine, Zealand University Hospital, Koege, +45 47326451, lmp@regionsjaelland.dk
Scientific contact	Lone Musaeus Poulsen, Department of Anaesthesia and intensive Care Medicine, Zealand University Hospital, Koege, +45 47326451, lmp@regionsjaelland.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	31 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2023
Global end of trial reached?	Yes
Global end of trial date	31 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess benefits and harms of haloperidol in adult, critically ill patients with delirium in the ICU. The primary objective is to determine, if haloperidol treatment in ICU patients with delirium will increase the number of days alive out of the hospital within 90 days. This primary objective includes 90 days mortality and length of hospital stay within 90 days after randomisation.

Protection of trial subjects:

The enrollment of patients was predominantly allowed as an emergency procedure because all the patients lacked the capacity to provide consent owing to delirium. Consent or assent was obtained from a physician independent of the trial (who represented the patient as a legal guardian) before enrollment of the patient, after which oral and written informed consent to continue participation was obtained from a relative or an authorized representative of the patient and later from the patient after the capacity to provide informed consent had returned. If consent was withdrawn, the assigned haloperidol or placebo was discontinued, and permission was sought to continue collection of trial data for analysis in accordance with national regulations. An independent data and safety monitoring committee assessed safety in an interim analysis, which was performed when 500 patients had been followed for 90 days. The trial was approved by ethic committees, national health authoritees and dataprotection agencies in particip

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2018
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	United Kingdom: 7
Country: Number of subjects enrolled	Denmark: 964
Country: Number of subjects enrolled	Finland: 28
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	1000
EEA total number of subjects	993

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)	302
From 65 to 84 years	652
85 years and over	46

Subject disposition

Recruitment

Recruitment details:

Patients 18 years of age or older who had been admitted to an ICU for an acute condition and had received a positive result on a screening test for delirium according to either the Confusion Assessment Method for the ICU (CAM-ICU)12 or the Intensive Care Delirium Screening Checklist (ICDSC) were assessed for eligibility.13

Pre-assignment

Screening details:

Exclusion criteria
- Contraindications to haloperidol
- Habitual treatment with antipsychotics
- Permanently incompetent
- Delirium assessment non-applicable
- Withdrawal from active therapy
- Fertile women with a positive urin hCG
- Patient under coercive measures
- Patients suffering from delirium tremens.
- Consent according to natio

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, Data analyst, Carer, Assessor

Blinding implementation details:

Clinicians, patients, investigators, outcome assessors, statisticians, and members of the data and safety monitoring committee were unaware of the trial-group assignments. Haloperidol and placebo were contained in identical ampules with identical labeling. The solutions were colorless and indistinguishable from each other

Arms

Are arms mutually exclusive?	Yes
Arm title	Haloperidol

Arm description:

2,5mg haloperidol x 3 daily with as needed dosing up to a maximum of 20 mg.

Arm type	Experimental
Investigational medicinal product name	Haloperidol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

2,5mg haloperidol x 3 daily with possibility of as needed doses up to a maximum of 20mg daily.

Arm title	Placebo

Arm description:

Normal saline

Arm type	Placebo

Investigational medicinal product name	Normal saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravascular use

Dosage and administration details:

Corresponding to active drug

Number of subjects in period 1	Haloperidol	Placebo
Started	510	490
Completed	501	486
Not completed	9	4
did not receive the intervention	9	4

Baseline characteristics

Reporting groups	
Reporting group title	Haloperidol
Reporting group description:	
2,5mg haloperidol x 3 daily with as needed dosing up to a maximum of 20 mg.	
Reporting group title	Placebo
Reporting group description:	
Normal saline	

Reporting group values	Haloperidol	Placebo	Total
Number of subjects	510	490	1000
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	164	138	302
From 65-84 years	327	325	652
85 years and over	19	27	46
Age continuous			
Units: years			
median	70	71	
inter-quartile range (Q1-Q3)	62 to 76	63 to 76	-
Gender categorical			
No. of females			
Units: Subjects			
Female	182	162	344
Male	328	328	656

End points

End points reporting groups

Reporting group title	Haloperidol
Reporting group description:	
2,5mg haloperidol x 3 daily with as needed dosing up to a maximum of 20 mg.	
Reporting group title	Placebo
Reporting group description:	
Normal saline	

Primary: Days alive and out of hospital to day 90

End point title	Days alive and out of hospital to day 90
End point description:	
End point type	Primary
End point timeframe:	
90 days	

End point values	Haloperidol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	491	472		
Units: days				
arithmetic mean (confidence interval 95%)	35.8 (32.9 to 38.6)	32.9 (29.9 to 35.8)		

Statistical analyses

Statistical analysis title	Intention to treat
Statistical analysis description:	
All analyses were adjusted for stratification variables (trial site and delirium motor subtype). In the primary analysis, we used a linear-regression model to estimate the adjusted mean difference between the groups. Because of the nonnormal distribution, we bootstrapped 95% confidence intervals; 50,000 resampling iterations were used in the bootstrap.	
Comparison groups	Haloperidol v Placebo
Number of subjects included in analysis	963
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22 [1]
Method	see comment
Parameter estimate	Mean difference (net)
Point estimate	2.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	7

Notes:

[1] - The Kryger Jensen and Lange16 test was used to estimate the P value because this test was designed for distributions of outcome results that show many patients with a value of zero.

Primary: Mortality

End point title	Mortality

End point description:

End point type	Primary

End point timeframe:

90

End point values	Haloperidol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	501	486		
Units: Number	182	210		

Statistical analyses

Statistical analysis title	Intention to treat
Comparison groups	Haloperidol v Placebo
Number of subjects included in analysis	987
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	-6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	-0.6

Primary: Length of hospital stay

End point title	Length of hospital stay

End point description:

End point type	Primary

End point timeframe:

90

End point values	Haloperidol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	491	472		
Units: days				
arithmetic mean (confidence interval 95%)	28.8 (26.7 to 30.8)	26.4 (24.4 to 28.5)		

Statistical analyses

Statistical analysis title	Intention to treat
Comparison groups	Haloperidol v Placebo
Number of subjects included in analysis	963
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Kryger-Lange test
Parameter estimate	Mean difference (final values)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	5.1

Secondary: Days alive without delirium or coma

End point title	Days alive without delirium or coma
End point description:	
Number of days a patient is alive and CAM-ICU negative	
End point type	Secondary
End point timeframe:	
90 days post-randomization	

End point values	Haloperidol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	490[2]	466[3]		
Units: days				
number (confidence interval 99%)	57.7 (53.4 to 62.2)	52.6 (48.0 to 57.1)		

Notes:
[2] - 20 had incomplete delirium screenings
[3] - 24 had incomplete CAM-ICU screenings

Statistical analyses

No statistical analyses for this end point

Secondary: Days alive without mechanical ventilation

End point title	Days alive without mechanical ventilation

End point description:

End point type	Secondary

End point timeframe:
90 days post-randomization

End point values	Haloperidol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	500	476		
Units: days				
number (confidence interval 99%)	57.9 (53.7 to 62.2)	53.9 (49.5 to 58.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serious Adverse Reactions in ICU

End point title	Serious Adverse Reactions in ICU

End point description:

End point type	Secondary

End point timeframe:
90 days post-randomization

End point values	Haloperidol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	501	486		
Units: patients	11	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Use of rescue medication

End point title	Use of rescue medication

End point description:

End point type	Secondary

End point timeframe:

90 days post-randomization

End point values	Haloperidol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	501	486		
Units: patients	288	302		

Statistical analyses

No statistical analyses for this end point

Secondary: Days with rescue medication

End point title	Days with rescue medication

End point description:

End point type	Secondary

End point timeframe:

90 days post-randomization

End point values	Haloperidol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	501	486		
Units: days				
number (confidence interval 99%)	2.9 (2.3 to 3.5)	2.9 (2.3 to 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: One-year mortality

End point title	One-year mortality

End point description:

End point type	Secondary

End point timeframe:

1 year post-randomization

End point values	Haloperidol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	491	471		
Units: patients	214	236		

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-VAS (health-related quality of life)

End point title	EQ-VAS (health-related quality of life)

End point description:

End point type	Secondary

End point timeframe:

1 year post-randomization

End point values	Haloperidol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	501[4]	486[5]		
Units: points				
number (confidence interval 95%)	25 (0.0 to 75)	3.3 (0.0 to 75)		

Notes:

[4] - Multiply imputed data was used and deceased patients was assigned wirst possible value

[5] - Multiply imputed data was used and deceased patients was assigned wirst possible value

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L Index values

End point title	EQ-5D-5L Index values

End point description:

End point type	Secondary

End point timeframe:

1 year post-randomization

End point values	Haloperidol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	501[6]	486		
Units: points				
number (confidence interval 95%)	0.3 (0.0 to 0.88)	0 (0.0 to 0.83)		

Notes:

[6] - Multiply imputed data was used and deceased patients was assigned wirst possible value

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
90 days post-randomisation	
Adverse event reporting additional description:	
Serious Adverse Reactions to haloperidol	
Assessment type	Systematic

Dictionary used	
Dictionary name	none
Dictionary version	0

Reporting groups	
Reporting group title	Serious Adverse Reactions Haloperidol
Reporting group description: -	
Reporting group title	Serious Adverse Reaction Placebo
Reporting group description: -	

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: Justification: The trial did not record non-serious adverse event in accordance with and justified in the protocol.

Serious adverse events	Serious Adverse Reactions Haloperidol	Serious Adverse Reaction Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 501 (2.20%)	9 / 486 (1.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Arytmia	Additional description: Occurence of VT or VF		
subjects affected / exposed	5 / 501 (1.00%)	4 / 486 (0.82%)	
occurrences causally related to treatment / all	5 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Tardive dyskinesia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrapyramidal disorder			
subjects affected / exposed	3 / 501 (0.60%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroleptic malignant syndrome			

subjects affected / exposed	0 / 501 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Anaphylaxia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 501 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 501 (0.20%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.1 %

Non-serious adverse events	Serious Adverse Reactions Haloperidol	Serious Adverse Reaction Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 501 (0.00%)	0 / 486 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported