Clinical trial results:
REmimazolam infusion in the context of Hypnotic Shortage in the Critical care Unit during the pandemic of COVID-19. The non-randomized, non-controlled, pilot, open, mono-centric REHSCU study.

Summary

EudraCT number	2020-003689-37
Trial protocol	FR
Global end of trial date	24 October 2021

Results information

Result version number	v1 (current)
This version publication date	01 January 2023
First version publication date	01 January 2023
Summary attachment (see zip file)	Final report_summary (REHSCU_Résume du rapport final_sign.pdf)

Trial information

Trial identification

Sponsor protocol code	RC20_0319

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04611425
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU de Nantes
Sponsor organisation address	1 place Alexis Ricordeau, Nantes, France,
Public contact	Direction Recherche et Innovation, CHU de Nantes, +33 0253482835, bp-prom-regl@chu-nantes.fr
Scientific contact	Direction Recherche et Innovation, CHU de Nantes, +33 0253482835, bp-prom-regl@chu-nantes.fr

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	04 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to assess the balance safety-efficacy of Remimazolam in the ICU during the first 8 hours after the beginning of infusion.

Protection of trial subjects:

Remimazolam is a novel benzodiazepine with promising pharmacokinetic and pharmacodynamic properties. It has been used in hundreds of patients worldwide in major cardiac and non-cardiac surgeries involving co-morbid patients, and in the critical care theatre. The safety data are extremely reassuring. The benefit/risk balance of the REHSCU study, in order to confirm the safety and efficacy of Remimazolam in the ICU in the context of a major hypnotic shortage in the setting of the COVID-19 pandemic, is highly favourable.

Background therapy:

The worldwide COVID-19 pandemic has led to a dramatic increase in the number of patients hospitalized in intensive care units for an acute respiratory failure in all countries. This situation has quickly led to massive shortages in masks, mechanical ventilation machines and common medications such as hypnotics. The reasons for such shortages are multiple: dramatic increase of the demand, production discontinuation because of shutdowns in multiple countries, and withholding of products by producing countries. All countries over the world are currently experiencing a major shortage in basic hypnotic medications (propofol, midazolam) in the intensive care as well as in the operating theatre. Remimazolam is a novel benzodiazepine with a very short half-life that has been administered in patients undergoing major surgery, as well as in the intensive care unit. We propose to perform a pilot study assessing the benefit-risk ratio of Remimazolam in our critical care units during the COVID-19 pandemic.

Evidence for comparator:

Non applicable.

Actual start date of recruitment	30 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	France: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	22
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

With the inclusion criteria we have adopted, thirty patients will therefore be required.
Inclusion : 11 months.
Follow-up : 5 days.

Pre-assignment

Screening details:

- Next-of-kin, Legal representative written informed consent or emergency consent
- Affiliation with French social security system or beneficiary from such system

Period 1

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

Arms

Arm title	Remimazolam

Arm description:

Remimazolam (CNS 7056) is a novel benzodiazepine. It is administered via a catheter (central or peripheric) intra-venously.
Patients will receive Remimazolam for a maximum of 48 hours after the beginning of infusion. Sedation may be interrupted any time, if the patient no longer needs general anaesthesia. The attending physician will be responsible for this decision.

Arm type	Experimental
Investigational medicinal product name	Remimazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

the initial dose of infusion will be within a 0.2-0.5 mg/min range. The dose of Remimazolam will be adapted to our protocol of sedation-analgesia protocol. The maximum dose of Remimazolam will be set at 1 mg/min.

Number of subjects in period 1	Remimazolam
Started	30
Completed	30

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
All patients received Remimazolam.	

Reporting group values	Overall Trial	Total	
Number of subjects	30	30	
Age categorical 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)	22	22	
From 65-84 years	8	8	
85 years and over	0	0	
Age continuous Units: years			
median	59.5		
full range (min-max)	21 to 82	-	
Gender categorical			
30 patients were recruited, 23 men and 7 women.			
Units: Subjects			
Female	7	7	
Male	23	23	

End points

End points reporting groups

Reporting group title	Remimazolam

Reporting group description:

Remimazolam (CNS 7056) is a novel benzodiazepine. It is administered via a catheter (central or peripheric) intra-venously.
Patients will receive Remimazolam for a maximum of 48 hours after the beginning of infusion. Sedation may be interrupted any time, if the patient no longer needs general anaesthesia. The attending physician will be responsible for this decision.

Primary: Efficacy

End point title	Efficacy[1]

End point description:

Sedation event: the investigator will check if Remimazolam provides an adequate level of sedation assessed with the Richmond Assessment Sedation Scale. The level of sedation will be set by the attending physician and is usually set at-1/0. The investigator will also monitor the need to use standard hypnotic drugs within this time frame as further medication (propofol, midazolam, dexmedetomidine) in case of Remimazolam inefficacy (Richmond
Assessment Sedation Scale).

End point type	Primary

End point timeframe:

8 hours after the beginning of infusion

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: it is a description of the study

End point values	Remimazolam			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage	30			

Statistical analyses

No statistical analyses for this end point

Primary: Safety

End point title	Safety[2]

End point description:

Cardiovascular event: Hypotension will be defined as a Mean Arterial Pressure ≤65mmHg or an increase ≥50% of the dose of norepinephrine (if appropriate), sustained over one hour after the beginning of Remimazolam.

End point type	Primary

End point timeframe:

8 hours after the beginning of infusion

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: it is a description of the study

End point values	Remimazolam			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Biological data

End point title	Biological data

End point description:

Routine laboratory tests

End point type	Secondary

End point timeframe:

4 days

End point values	Remimazolam			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage	30			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

5 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Vascular access site complication	Additional description: venotoxicity		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 30 (70.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hepatic enzyme abnormal			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Mean arterial pressure decreased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Troponin increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Endotracheal intubation complication			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
Thrombophlebitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Atrial fibrillation			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Bradycardia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Hyperleukocytosis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 1		
Gastrointestinal disorders Large intestine perforation subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 1		
Infections and infestations Pneumonia subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2021	Addition of an emergency procedure for patient inclusion Extension of the recruitment period by an additional 12 months
06 May 2021	Update of the relative's information note following the implementation of the emergency procedure
02 July 2021	Changement de PI sur site

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported.

Notes: