Clinical trial results:
CONTROLLED, DOUBLE-BLIND, RANDOMIZED CLINICAL TRIAL FOR PROPHILAXIS OF POSOPERATIVE DELIRIUM IN HIGH RISK SURGICAL PATIENTS WITH QUETIAPINE.

Summary

EudraCT number	2016-004117-27
Trial protocol	ES
Global end of trial date	07 June 2022

Results information

Result version number	v1 (current)
This version publication date	01 November 2022
First version publication date	01 November 2022

Trial information

Trial identification

Sponsor protocol code	QUEPRO

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03739476
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundación IECSCYL-IBSAL.
Sponsor organisation address	Paseo de San Vicente, 58-182., Salamanca, Spain, 37007
Public contact	Unidad de gestión de ensayos clínicos, IBSAL, 34 923210960, ensayosclinicos@ibsal.es
Scientific contact	Unidad investigación clínica y ensayos clínicos, IBSAL, 696022264 923291100 ext 55779, uicec.gestion@ibsal.es

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	07 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2020
Global end of trial reached?	Yes
Global end of trial date	07 June 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To Know the incidence of postoperative delirium in patients at risk, over 65 years, treated early with prophylactic quetiapine versus placebo.

Protection of trial subjects:

Adequate information of each patient and efficient monitoring of treatment safety through pharmacovigilance.

Background therapy:

Postoperative delirium is a prevalent condition which worsens the outcomes of elderly patients at surgery. Nowadays there are not specifics treatments for this illness. For decades, antipsychotic medication has been used to control the symptoms.

Evidence for comparator:

Quetiapine is a second-generation antipsychotic which has been used to control delirious symptoms, but there is not evidence about this use in prophylaxis of the disease.

Actual start date of recruitment	13 March 2019
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	Spain: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	0

From 65 to 84 years	44
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

The subjects were recruited if they were greater than or equal to 65 years-old patients who will be undergoing major surgery (noncardiac-with a hospitalization more than three days) and having an equal or greater score of 5 on the scale Delphi.
The patient had to be able to understand all the information provided and sing the informed consent.

Pre-assignment

Screening details:

With these criteria, 79 patients were evaluated from January 2019 until March 2020 and finally 54 were included in trial. There was a low recruitment rate because the number of patients available were lower than expected

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Active group

Arm description:

Patients treated with the medicinal product

Arm type	Experimental
Investigational medicinal product name	Quetiapine
Investigational medicinal product code	N05AH04
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A capsule with 25mg was administrated twice daily, starting after surgery for three days

Arm title	Placebo group

Arm description:

Patients treated with the placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A capsule with placebo was administrated twice daily, starting after surgery for three days

Number of subjects in period 1	Active group	Placebo group
Started	31	23
Completed	27	21
Not completed	4	2
Consent withdrawn by subject	3	1
Physician decision	1	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	54	54	
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)	0	0	
From 65-84 years	44	44	
85 years and over	10	10	
Age continuous Units: years			
median	81		
inter-quartile range (Q1-Q3)	75 to 83	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	40	40	

End points

End points reporting groups

Reporting group title	Active group
Reporting group description:	
Patients treated with the medicinal product	
Reporting group title	Placebo group
Reporting group description:	
Patients treated with the placebo	

Primary: Delirium incidence

End point title	Delirium incidence[1]
End point description:	
Number of patients diagnosed with delirium within the first four days after taking medication.	
End point type	Primary
End point timeframe:	
24h, 48h, 72h, 96h	

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: This trial, despite the huge efforts of the group of researchers had to be ended prematurely. In this situation, statistical analysis is not reliable due to the inability to reach the expected "n".
The number of patients recruited is not sufficient to perform a viable statistical analysis.

End point values	Active group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	23		
Units: patients				
24h-1stvisit	0	0		
48h-2ndvisit	3	0		
72h-3rdvisit	3	1		
96h-4thvisit	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

28(±2) days since the beginning of treatment

Adverse event reporting additional description:

All the severe adverse events were not related to the drug under study. The elevate age and mayor surgery of the selected cohort for this trial can be related to the number of adverse events detected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Active group

Reporting group description:

Patients treated with the medicinal product: quetiapine

Reporting group title	Placebo group

Reporting group description:

Patients treated with the placebo

Serious adverse events	Active group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 31 (9.68%)	5 / 23 (21.74%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Intestinal perforation			
subjects affected / exposed	1 / 31 (3.23%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal abscess			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Non ST segment elevation acute coronary syndrome			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Diarrhea clostridium			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound evisceration			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exacerbation of COPD			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory insufficiency			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 31 (3.23%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis secondary			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (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: 0 %

Non-serious adverse events	Active group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 31 (35.48%)	5 / 23 (21.74%)	
Surgical and medical procedures			
Post procedural urine leak			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Paralytic ileus			
subjects affected / exposed	3 / 31 (9.68%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal bleeding			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Postoperative wound complication			
subjects affected / exposed	2 / 31 (6.45%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Gonarthritis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Diarrhea			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute urine retention			
subjects affected / exposed	2 / 31 (6.45%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Anaemia postoperative			
subjects affected / exposed	3 / 31 (9.68%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Psychiatric disorders			
Agitation mental			
subjects affected / exposed	1 / 31 (3.23%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Acute delirium			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	

Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 23 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2019	To solve the problem of the low rate recruitment, the authors of the Delphi scale were contacted, requesting the complete data of the original work. After careful study, it was concluded that a lower cut-off point could allow an increase in the recruitment rate. After performing the relevant calculations, it was determined that a value of five on the Delphi scale allows to discriminate patients at risk against patients without risk with a sensitivity of 85% (95% CI: 78.49-93.23), a specificity of 80% (95% CI: 76.16-83.75) and an accuracy of 81%, with an area under the calculated curve of 0.83 (95% CI: 0,79-0,87)so it is still excellent, in addition to allowing to considerably increase the chances of recruiting patients within the target population. Therefore the proposed and accepted changes by Agencia Española de Medicamento y Productos Sanitarios (AEMPS) in the new version of the protocol were: 1) Inclusion criteria: Version 1.7: Patients over or equal to 65 years of age who are undergoing major non-cardiac surgery and who have a score equal to or greater than 7 on the Delphi scale. Version 2.0: Patients over or over 65 years of age who are undergoing major non-cardiac surgery and who have a score equal to or greater than 5 on the Delphi scale. 2) Exclusion criterion: Version 1.7: Patients at risk of developing delirium on admission. Version 2.0: Patients with a score of less than 5 on the Delphi scale -Extension of the total time of the clinical trial based on the extension in the recruitment period of 18 months, until expiration of the medication (June 30, 2020). Medication undergoes a process to guarantee the blind, one of the pillars of the study. It is not possible to generate new medication due to lack of financial funds.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 June 2020	It was impossible to continuate the trial because of the crisis SARS-COV-2 pandemic. This exceptional situation forced to suspend the non-essential scheduled surgical activity and recruitment was stopped. On June 30,2020 medication expired and there was no possible to get more medication (because of lack of economical support and the global pandemic). This trial, despite the huge efforts of the group of researchers had to be ended prematurely. In this situation, statistical analysis is not reliable due to the inability to reach the expected “n”.	-

Notes:

Limitations and caveats

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

It was impossible to continuate the trial because of the crisis SARS-COV-2 pandemic.
This exceptional situation forced to suspend the non-essential scheduled surgical activity and recruitment was stopped.

Notes: