Clinical trial results:
Intratympanic injection of N-acetylcysteine for prevention of Cisplatine-induced ototoxicity

Summary

EudraCT number	2019-004463-44
Trial protocol	BE
Global end of trial date	03 September 2023

Results information

Result version number	v1 (current)
This version publication date	07 November 2023
First version publication date	07 November 2023

Trial information

Trial identification

Sponsor protocol code	CHUB-NAC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04226456
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Departement of ENT and head&neck surgery
Sponsor organisation address	Rue Haute 322, Brussels, Belgium,
Public contact	Gaëtan Cavelier, Department of ENT and Head&Neck Surgery of CHU Saint Pierre, 0032 02535 42 67, gaetan_cavelier@stpierre-bru.be
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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	03 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 September 2023
Global end of trial reached?	Yes
Global end of trial date	03 September 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate the protecting effect of Lysomucil® 10% against Cisplatin-induced ototoxicity. In this case, we will evaluate its effect through the transtympanic administration in both ears.

Protection of trial subjects:

Local anesthesia of the eardrum was made with xylocain 10% before the injection for patients in the interventional arm.
For those patients, tramadol 50mg sublingual was administered prior to the injection and could be given again after the injection if needed in order to control the pain induced by the IMP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 February 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	Belgium: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	14
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment started in February 2020, 7 months late because of SARS-CoV2 pandemic, and early end of recruitment was declared on 4th February 2023 because of poor accrual. The recruitment only occurred in Belgium, more specifically at CHU Saint-Pierre Hospital in Brussels.

Pre-assignment

Screening details:

Thirty-seven patients were assessed for eligibility. Of these, 19 were randomized. Nine patients refused to participate. 2 were not eligible because the oncologist changed the chemotherapy before the visit of eligibility and 7 had exclusion criteria.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	NAC (intervention)

Arm description:

Arm of intervention.
Patients received N-acetylcysteine injection during each cisplatin cycle.

Arm type	Experimental
Investigational medicinal product name	N-acetylcystein 10%
Investigational medicinal product code	
Other name	Lysomucil®
Pharmaceutical forms	Injection
Routes of administration	Auricular use

Dosage and administration details:

N-acetylcysteine 10% was administered through transtympanic injection using a 26-gauge syringe until the middle ear of both ears was filled (0.4-1ml). The injections were administered 40 to 60 minutes maximum prior to each Cisplatin cycle. After the injection, patients remained motionless in a neutral head position with the thorax elevated 30° for horizontal position for 30 to 40 minutes.

Arm title	Control arm

Arm description:

Control arm.
Patients did not receive any other treatment during cisplatin cycle.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	NAC (intervention)	Control arm
Started	10	9
Completed	5	6
Not completed	5	3
Consent withdrawn by subject	3	-
Deceased by main disease	1	2

excluded because in another clinical trial	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	57.2		
standard deviation	± 10.9	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	15	15	

End points

End points reporting groups

Reporting group title	NAC (intervention)
Reporting group description:	
Arm of intervention. Patients received N-acetylcysteine injection during each cisplatin cycle.	
Reporting group title	Control arm
Reporting group description:	
Control arm. Patients did not receive any other treatment during cisplatin cycle.	

Primary: Ototoxicity

End point title	Ototoxicity
End point description:	
Primary endpoint is the apparition of ototoxicity (taken as a binary indicator) as defined by the International Common Terminology Criteria for Adverse Events (CTCAE), version 5: - A Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear - and/or the apparition of a tinnitus (not previously present).	
End point type	Primary
End point timeframe:	
The primary endpoint was measured at 6 months after the last Cisplatin cycle and compared to the baseline between the two arms.	

End point values	NAC (intervention)	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Presence or absence				
Presence	3	3		
Absence	2	3		

Statistical analyses

Statistical analysis title	Ototoxicity analysis
Statistical analysis description:	
The presence of ototoxicity at 6 months after the last cycle of Cisplatin baseline was reported as a proportion with its exact 95% confidence interval. The statistical significance of the results was measured by the Fisher's Exact Test of Independence. The appearance of an ototoxicity (taken as a binary indicator) was defined using the CTCAE, V.5: a threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear, and/or the appearance of a tinnitus.	
Comparison groups	Control arm v NAC (intervention)

Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event assessment was made throughout the period of the trial.
We started on the date of the first patient "in" until the declaration of end of trial.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	5

Reporting groups

Reporting group title	NAC arm
Reporting group description: -	
Reporting group title	Control arm

Reporting group description: -

Serious adverse events	NAC arm	Control arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 9 (66.67%)	6 / 8 (75.00%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	5 / 9 (55.56%)	2 / 8 (25.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
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			
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	1 / 9 (11.11%)	2 / 8 (25.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Massive hemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 9 (22.22%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforated ulcer			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-induced colitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
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			
COVID-19 pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Skin and subcutaneous tissue disorders			
Mucosal erosion			
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Immune-induced diabetes			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unknown infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dysphagia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nutritional condition abnormal	Additional description: denutrition with need of hospitalisation		
subjects affected / exposed	1 / 9 (11.11%)	3 / 8 (37.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NAC arm	Control arm	
Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 9 (100.00%)	7 / 8 (87.50%)	
Cardiac disorders Hypertension subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 8 (12.50%) 3	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) Pulsatile Tinnitus subjects affected / exposed occurrences (all)	8 / 9 (88.89%) 10 2 / 9 (22.22%) 2	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Odynophagia subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) xerostomia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 0 / 9 (0.00%) 0	2 / 8 (25.00%) 3 2 / 8 (25.00%) 2 3 / 8 (37.50%) 3 1 / 8 (12.50%) 1	
Metabolism and nutrition disorders Denutrition subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 8 (12.50%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2021	1) Protocol version 3.0 dated 03 May 2021: We decided to modify our exclusion criteria as they excluded to many patients and were not consistent with our clinical practice. Indeed, N-acetylcystein (NAC) has demonstrated protective effects against cisplatin induced ototoxicity in previous clinical trials (ref 14,15 of the protocol). In these trials, only one ear was injected with N-acetylcystein while the other was control or receiving another drug. In these studies, authors excluded patients with middle ear disease or eardrum perforation. We have begun our trial with 2 of our exclusion criteria: - Pathological findings on otoscopy that do not allow safe intratympanic drug delivery and reliable distortion product otoacoustic emissions (DPOAEs) testing. - Conductive hearing loss > 10dBHL. The problem of those criteria is that we had to exclude patients with serous media otitis. However, patients with rhinopharynx carcinoma often suffer from this condition and need transtympanic drainage to restore their hearing. The primary objective of our trial is to evaluate the protecting effect of NAC 10% against Cisplatin-induced ototoxicity. In this case, we will evaluate its effect through the transtympanic administration in both ears. If the treatment is contributive, we aim to implement it as the future gold standard to prevent cisplatin induced ototoxicity. In order to do it, we need to show that the treatment is effective in clinical practice. In clinical practice, the first line of treatment of patient with rhinopharynx treatment is radiotherapy and radiochemotherapy with cisplatin. Therefore, we deleted the exclusion by the impossibility to allow reliable DPOAEs testing as with a transtympanic drainage, DPOAEs will often be impossible to test. We decided to extend to conductive hearing loss up to 20 dBHL as patients with tympanic drainage will often have a small conductive hearing loss less than 20 dBHL. 2) The reference safety information was updated for NAC.

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.

The major limitation of our trial in the small number of patients recruited and a higher dropout rate than expected. Only half of the patients recruited completed the study. The SARS-Cov2 pandemic delayed the recruitment beginning.

Notes: