Clinical trial results:
An investigation of postoperative pain, why still in hospital and days alive and out of hospital following transoral robotic surgery for squamous cell carcinoma of unknown primary and obstructive sleep apnea

Summary

EudraCT number	2019-004610-34
Trial protocol	DK
Global end of trial date	09 November 2022

Results information

Result version number	v1 (current)
This version publication date	28 October 2023
First version publication date	28 October 2023

Trial information

Trial identification

Sponsor protocol code	DexaCup

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04189107
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet
Sponsor organisation address	Inge Lehmanns vej, Copenhagen, Denmark,
Public contact	Mikkel Larsen, Rigshospitalet, Department of Otorhinolaryngology, Head and Neck Surgery & Audiology, 45 35452071, mikkel.hjordt.holm.larsen@regionh.dk
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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	02 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 November 2022
Global end of trial reached?	Yes
Global end of trial date	09 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of high dose steroids on the postoperative pain level measured by self-assessed VAS during rest and swallowing following transoral robotic surgery

Protection of trial subjects:

Dexamethasone is a commonly used and safe drug used to reduce PONV. The analgesic effect of dexamethasone has previously only been sparsely studied in patients undergoing transoral robotic surgery. In this RCT we compared the effect of high vs low dose dexamethasone on patient reported pain. All adverse effects were monitored and reported. patients with contraindications for dexamethasone therapy were not included. The trial was monitored by the local GCP unit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2020
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: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	13
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was included and randomized 17th of August 2020 and the last patient was included and randomized 13th of October 2022. A total of 18 patients were included and randomized with 9 patients in each arm

Pre-assignment

Screening details:

a total of 22 patients were screened. 4 patients were excluded as they declined participation or fulfilled a exclusion criteria

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	Investigator, Monitor, Assessor, Subject

Blinding implementation details:

Dexamethasone was delivered in blinded packages from a pharmacy. thus the treatment was blinded to all involved personnel and subjects.

Arms

Are arms mutually exclusive?	Yes
Arm title	High dose

Arm description:

Patients undergoing transoral robotic resection lingual tonsillectomy as part of the diagnostic workup for carcinoma of unknown primary or in the treatment of obstructive sleep apnea were randomized to either 24 mg dexamethasone intraoperatively vs 8 mg intraoperatively followed by either 12mg on pod2 and pod 4 vs placebo on pod2 and pod4.

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

Dosage and administration details:

the solution was delivered in 4mg/ml dexamethasone. Patient in the high dose group thus received 6mL intraoperatively and 3mL on POD2 and 4. patients in the low dose group received 2mL intraoperatively and placebo (sodium chloride) 4mL followed by 3 mL of sodium chloride on POD2 and 4

Arm title	low dose

Arm description:

Patients undergoing transoral robotic resection lingual tonsillectomy as part of the diagnostic workup for carcinoma of unknown primary or in the treatment of obstructive sleep apnea were randomized to either 24 mg dexamethasone intraoperatively vs 8 mg intraoperatively followed by either 12mg on pod2 and pod 4 vs placebo on pod2 and pod4.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	High dose	low dose
Started	9	9
Completed	9	9

Baseline characteristics

Reporting groups	
Reporting group title	High dose
Reporting group description:	
Patients undergoing transoral robotic resection lingual tonsillectomy as part of the diagnostic workup for carcinoma of unknown primary or in the treatment of obstructive sleep apnea were randomized to either 24 mg dexamethasone intraoperatively vs 8 mg intraoperatively followed by either 12mg on pod2 and pod 4 vs placebo on pod2 and pod4.	
Reporting group title	low dose
Reporting group description:	
Patients undergoing transoral robotic resection lingual tonsillectomy as part of the diagnostic workup for carcinoma of unknown primary or in the treatment of obstructive sleep apnea were randomized to either 24 mg dexamethasone intraoperatively vs 8 mg intraoperatively followed by either 12mg on pod2 and pod 4 vs placebo on pod2 and pod4.	

Reporting group values	High dose	low dose	Total
Number of subjects	9	9	18
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)	6	7	13
From 65-84 years	3	2	5
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	58.22	56.56	
standard deviation	± 11.84	± 12.34	-
Gender categorical Units: Subjects			
Female	0	1	1
Male	9	8	17
TORS indication Units: Subjects			
CUP	6	8	14
OSAS	3	1	4
Smoking status Units: Subjects			
0-10 pack-years	4	5	9
>10 pack years	4	3	7
unknown	1	1	2
Alcohol consumption Units: Subjects			
>14 units(men)/>7 units(women)	0	1	1

</=14 units(men)/</=7 units (women)	6	7	13
unknown	3	1	4

Charlton comorbidity index			
Units: CCI			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 0	-
Preoperative VAS rest morning			
Units: VAS			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 2	-
Preoperative VAS swallowing morning			
Units: VAS			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 1	0 to 1	-
Preoperative VAS rest evening			
Units: VAS			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 1	-
Preoperative VAS swallowing evening			
Units: VAS			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 1	0 to 1	-
TORS Duration			
Units: minute			
median	60.0	67	
inter-quartile range (Q1-Q3)	45 to 66	54 to 114	-

End points

End points reporting groups

Reporting group title	High dose

Reporting group description:

Patients undergoing transoral robotic resection lingual tonsillectomy as part of the diagnostic workup for carcinoma of unknown primary or in the treatment of obstructive sleep apnea were randomized to either 24 mg dexamethasone intraoperatively vs 8 mg intraoperatively followed by either 12mg on pod2 and pod 4 vs placebo on pod2 and pod4.

Reporting group title	low dose

Reporting group description:

Patients undergoing transoral robotic resection lingual tonsillectomy as part of the diagnostic workup for carcinoma of unknown primary or in the treatment of obstructive sleep apnea were randomized to either 24 mg dexamethasone intraoperatively vs 8 mg intraoperatively followed by either 12mg on pod2 and pod 4 vs placebo on pod2 and pod4.

Primary: VAS

End point title	VAS[1]

End point description:

End point type	Primary

End point timeframe:

Until postoperative day 14

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: The median VAS for each group at measure point was compared with Mann Whitney U-test. no statistical analyses has been added in the result section, as only one p value can be reported.

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: VAS				
median (inter-quartile range (Q1-Q3))				
Day of surgery, evening rest	4 (0 to 5)	2.5 (1.5 to 3)		
day of surgery, evening swallow	5 (1 to 7)	3.25 (1 to 4)		
POD1, rest morning	3 (0 to 5)	2 (2 to 4)		
POD1, swallow morning	5 (1 to 7)	4 (3.5 to 5)		
POD1, rest evening	3 (0 to 6)	2 (2 to 4)		
POD1, swallow evening	4 (2 to 8)	4 (4 to 5)		
POD2, rest morning	3 (1 to 5)	2 (2 to 4)		
POD2, swallow morning	5 (3 to 6)	5 (4 to 6)		
POD2, rest evening	3 (1 to 4)	2.5 (2 to 6)		
POD2, swallow evening	4 (3 to 4)	5 (3 to 7)		
POD3, rest morning	3 (1 to 5)	4 (2 to 5)		
POD3, swallow morning	4 (4 to 5)	6 (3 to 7)		
POD3, rest evening	3 (2 to 4)	3.5 (2 to 5)		
POD3, swallow evening	4 (4 to 5)	6 (3 to 7)		
POD4, rest morning	4 (2 to 7)	3.5 (2 to 5)		
POD4, swallow morning	5 (4 to 7)	6 (4 to 7)		

POD4, rest evening	4 (2 to 6)	3 (2 to 6)		
POD4, swallow evening	4 (3 to 7)	6 (5 to 7)		
POD5, rest morning	4 (2 to 7)	3 (2 to 5)		
POD5, swallow morning	5 (4 to 8.5)	5 (4 to 7)		
POD5, rest evening	4 (2 to 7)	3 (2 to 6)		
POD5, swallow evening	4 (3 to 7)	6 (5 to 7)		
POD6, rest morning	4 (3 to 7)	4 (3 to 6)		
POD6, swallow morning	6 (4 to 7)	6 (4.5 to 7.75)		
POD6, rest evening	4 (3 to 6)	4 (3 to 7)		
POD6, swallow evening	6 (4 to 7)	6.5 (5 to 7)		
POD7, rest morning	4 (3 to 7)	4 (2 to 7)		
POD7, swallow morning	5 (4 to 7)	6 (4.5 to 8)		
POD7, rest evening	4 (3 to 7)	5 (3 to 7)		
POD7, swallow evening	6 (4 to 8)	6 (5 to 8)		
POD8, rest morning	4 (4 to 6)	6 (3 to 7)		
POD8, swallow morning	6 (4 to 7)	6.5 (6 to 7)		
POD8, rest evening	4 (3 to 6)	6 (3 to 7)		
POD8, swallow evening	6 (4 to 7)	7 (6 to 7)		
POD9, rest morning	5 (3 to 8)	5 (3.8 to 7)		
POD9, swallow morning	6 (4 to 8)	6.7 (5 to 8)		
POD9, rest evening	5 (4 to 6)	6 (3 to 7)		
POD9, swallow evening	6 (5 to 6)	7 (5 to 7)		
POD10, rest morning	5 (2 to 6)	4 (3 to 5)		
POD10, swallow morning	6 (4 to 7)	5 (4 to 6)		
POD10, rest evening	4 (3 to 6)	3 (2.5 to 7)		
POD10, swallow evening	6 (4 to 6)	4 (4 to 7)		
POD11, rest morning	4 (3 to 5)	4 (2 to 6.5)		
POD11, swallow morning	5 (4 to 6)	4 (3 to 7)		
POD11, rest evening	3 (2 to 4)	4 (3 to 7)		
POD11, swallow evening	5 (3 to 5)	5 (4 to 7)		
POD12, rest morning	2 (2 to 4)	3 (2.5 to 4.5)		
POD12, swallow morning	4 (3 to 4)	4 (3 to 5.5)		
POD12, rest evening	3 (2 to 4)	2 (2 to 4)		
POD12, swallow evening	4 (3 to 4)	3 (3 to 5)		
POD13, rest morning	3 (2 to 3)	3 (1 to 5)		
POD13, swallow morning	3 (3 to 3)	4 (3 to 5)		
POD13, rest evening	2 (1.5 to 3)	2 (1.5 to 4)		
POD13, swallow evening	2 (2 to 3)	3 (3 to 5)		
POD14, rest morning	2 (1 to 2)	1 (1 to 4)		
POD14, swallow morning	2 (2 to 2)	3 (2 to 5)		
POD14, rest evening	1.5 (1 to 2)	2 (1 to 4)		
POD14, swallow evening	2 (2 to 2)	3 (2 to 4.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of stay

End point title	Length of stay

End point description:

End point type	Secondary

End point timeframe:
from day of surgery until discharge

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: day				
median (inter-quartile range (Q1-Q3))	4 (4 to 4)	4 (4 to 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rescue opioid use, during primary admission

End point title	Rescue opioid use, during primary admission

End point description:

End point type	Secondary

End point timeframe:
from day of surgery until discharge

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: mg				
median (inter-quartile range (Q1-Q3))	15 (0 to 66)	0 (0 to 70)		

Statistical analyses

No statistical analyses for this end point

Secondary: rescue opioid use, day of surgery until postoperative day 14

End point title	rescue opioid use, day of surgery until postoperative day 14

End point description:

End point type	Secondary

End point timeframe:
from day of surgery until postoperative day 14

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: mg				
median (inter-quartile range (Q1-Q3))	70 (30 to 270)	22.5 (0 to 120)		

Statistical analyses

No statistical analyses for this end point

Secondary: mortality

End point title	mortality

End point description:

End point type	Secondary

End point timeframe:
thirty day mortality

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: subjects				
yes	0	0		
no	9	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative hemorrhage

End point title	Postoperative hemorrhage

End point description:

End point type	Secondary

End point timeframe:
from day of surgery until followup

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: subjects				
yes	0	0		
no	9	9		

Statistical analyses

No statistical analyses for this end point

Secondary: postoperative nausea and vomitting

End point title	postoperative nausea and vomitting

End point description:

End point type	Secondary

End point timeframe:

Postoperative day 1-14

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: subjects				
Day 1-4	1	2		
day 5-7	2	2		
day 8-14	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative infection

End point title	Postoperative infection

End point description:

End point type	Secondary

End point timeframe:

From day of surgery until follow-up

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: subjects				
no infection	8	6		
infection treated with oral antibiotics	1	2		
infection treated with intravenous antibiotics	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood glucose level

End point title	Blood glucose level

End point description:

End point type	Secondary

End point timeframe:

Postoperative day 2 and 4

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: mmol/L				
median (inter-quartile range (Q1-Q3))				
Postoperative day 2	6.15 (5.25 to 6.75)	5.10 (4.8 to 5.7)		
postoperative day 4	5.2 (4.9 to 5.7)	4.85 (4.7 to 5.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tracheotomy placement

End point title	Tracheotomy placement

End point description:

End point type	Secondary

End point timeframe:
Day of surgery until postoperative day 30

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: subjects				
yes	0	0		
no	9	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Unplanned readmission

End point title	Unplanned readmission

End point description:

End point type	Secondary

End point timeframe:
Thirty day unplanned readmission rate

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Subjects				
yes	0	0		
no	9	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Naso gastic tube placement

End point title	Naso gastic tube placement

End point description:

End point type	Secondary

End point timeframe:
From day of surgery until removal

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: day				
median (inter-quartile range (Q1-Q3))	1 (1 to 4)	1 (1 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Feeding tube re-insertion

End point title	Feeding tube re-insertion

End point description:

End point type	Secondary

End point timeframe:

thirty day feeding tube re-insertion rate

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: subjects				
yes	0	0		
no	9	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Days until oral dietary intake

End point title	Days until oral dietary intake

End point description:

End point type	Secondary

End point timeframe:

from day of surgery until oral dietary intake

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: day				
median (inter-quartile range (Q1-Q3))	1 (1 to 1)	1 (1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported Food consistency

End point title	Patient reported Food consistency
End point description: Patient reported Food consistency	
End point type	Secondary
End point timeframe: POD1 until POD 14	

End point values	High dose	low dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: subjects	9	9		

Attachments (see zip file)	figure3.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

until 60 hours after last administration of study drug. SAE/SAR until postoperative day 14

Assessment type	Systematic

Dictionary used

Dictionary name	none
Dictionary version	0

Reporting groups

Reporting group title	ALL adverse events/reactions and SAE/SAR

Reporting group description: -

Serious adverse events	ALL adverse events/reactions and SAE/SAR		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	ALL adverse events/reactions and SAE/SAR		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 18 (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: There were no Adverse events or reactions or SAE/SAR in the cohort. The trial has a limited sample size, which can explain no adverse events

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2022	Sample size changed from 34 in total to 18 patients in total

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.

All patients in the CUP group were HPV+.

Notes: