Clinical trial results:
Effect of granisetron on facial skin sensitivity in healthy volunteers

Summary

EudraCT number	2013-000026-57
Trial protocol	SE
Global end of trial date	01 November 2018

Results information

Result version number	v1 (current)
This version publication date	04 April 2021
First version publication date	04 April 2021

Trial information

Trial identification

Sponsor protocol code	Gra-sensv1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Karolinska Institutet
Sponsor organisation address	17177, Stockholm, Sweden,
Public contact	Department of Dental medicine Malin Ernberg, Karolinska Institutet, 46 852488236, malin.ernberg@ki.se
Scientific contact	Department of Dental medicine Malin Ernberg, Karolinska Institutet, 46 852488236, malin.ernberg@ki.se

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	01 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2018
Global end of trial reached?	Yes
Global end of trial date	01 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of granisetron on facial skin sensitivity.

To clairify, this is a cross-over study with 3 arms, where the same 18 participants have been included in all 3 arms. This system is not made for the reporting of cross-over studies, therefore workarounds have been made in order to report the results as accurately as possible. Therefore, in the statistics section it looks like there are 36 participants included in each analysis, but the correct should be 18.

Protection of trial subjects:

The study was reviewed and approved by Regional Ethical Review Board in Stockholm, Sweden (Dnr 2013/932-31/4) Swedish Medical Products Agency (EudoraCT-number 2008-000746-32). The patients/participants provided their written informed consent to participate in this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 March 2014
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	Sweden: 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)	18
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at the Department of Dental Medicine, Karolinska Institutet, Huddinge, Sweden. Participants were recruited between March 2014 and November 2018. They were recruited by flyers posted at the Department of Dental Medicine, Karolinska Institutet, and at the library of Södertörn University, both in Huddinge, Sweden.

Pre-assignment

Screening details:

Inclusion criteria were: (a) age between 18 and 40 years, (b) good general health, and (c) male sex.

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

Blinding implementation details:

Randomization and distribution of injections were done by one of the researchers not participating in the data collection.

Arms

Are arms mutually exclusive?	No
Arm title	Baseline Granisetron (test-substance)

Arm description:

Test was done at baseline before 1ml of granisetron was injected into the skin over the masseter muscle.

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

Dosage and administration details:

1ml of granisetron was injected into the skin over the masseter muscle.

Arm title	Baseline Lidocaine (positive control)

Arm description:

Test was done at baseline before 1ml of Lidocaine was injected into the skin over the masseter muscle.

Arm type	Active comparator
Investigational medicinal product name	Lidocaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1ml of lidocaine was injected into the skin over the masseter muscle.

Arm title	Baseline Isotonic saline (placebo)

Arm description:

Test was done at baseline before 1ml of isotonic saline was injected into the skin over the masseter muscle.

Arm type	Placebo
Investigational medicinal product name	Isotonic saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1ml of sotonic saline was injected into the skin over the masseter muscle.

Arm title	5min Granisetron (test-substance)

Arm description:

Test was done at 5 min after 1ml of granisetron was injected into the skin over the masseter muscle.

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

Dosage and administration details:

1ml of granisetron was injected into the skin over the masseter muscle.

Arm title	5min Lidocaine (positive control)

Arm description:

Test was done at min 5 after 1ml of Lidocaine was injected into the skin over the masseter muscle.

Arm type	Active comparator
Investigational medicinal product name	Lidocaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1ml of lidocaine was injected into the skin over the masseter muscle.

Arm title	5min Isotonic saline (placebo)

Arm description:

Test was done at min 5 after 1ml of isotonic saline was injected into the skin over the masseter muscle.

Arm type	Placebo
Investigational medicinal product name	Isotonic saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1ml of sotonic saline was injected into the skin over the masseter muscle.

Arm title	20min Granisetron (test-substance)

Arm description:

Test was done at 20 min after 1ml of granisetron was injected into the skin over the masseter muscle.

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

Dosage and administration details:

1ml of granisetron was injected into the skin over the masseter muscle.

Arm title	20min Lidocaine (positive control)

Arm description:

Test was done at min 20 after 1ml of Lidocaine was injected into the skin over the masseter muscle.

Arm type	Active comparator
Investigational medicinal product name	Lidocaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1ml of lidocaine was injected into the skin over the masseter muscle.

Arm title	20min Isotonic saline (placebo)

Arm description:

Test was done at 20 min after 1ml of isotonic saline was injected into the skin over the masseter muscle.

Arm type	Placebo
Investigational medicinal product name	Isotonic saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1ml of sotonic saline was injected into the skin over the masseter muscle.

Arm title	40min Granisetron (test-substance)

Arm description:

Test was done at 40 min after 1ml of granisetron was injected into the skin over the masseter muscle.

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

Dosage and administration details:

1ml of granisetron was injected into the skin over the masseter muscle.

Arm title	40min Lidocaine (positive control)

Arm description:

Test was done at 40 min after 1ml of Lidocaine was injected into the skin over the masseter muscle.

Arm type	Active comparator
Investigational medicinal product name	Lidocaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1ml of lidocaine was injected into the skin over the masseter muscle.

Arm title	40min Isotonic saline (placebo)

Arm description:

Test was done at 40 min after 1ml of isotonic saline was injected into the skin over the masseter muscle.

Arm type	Placebo
Investigational medicinal product name	Isotonic saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1ml of sotonic saline was injected into the skin over the masseter muscle.

Arm title	60min Granisetron (test-substance)

Arm description:

Test was done at 60 min after 1ml of granisetron was injected into the skin over the masseter muscle.

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

Dosage and administration details:

1ml of granisetron was injected into the skin over the masseter muscle.

Arm title	60min Lidocaine (positive control)

Arm description:

Test was done at 60 min after 1ml of Lidocaine was injected into the skin over the masseter muscle.

Arm type	Active comparator
Investigational medicinal product name	Lidocaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1ml of lidocaine was injected into the skin over the masseter muscle.

Arm title	60min Isotonic saline (placebo)

Arm description:

Test was done at 60 min after 1ml of isotonic saline was injected into the skin over the masseter muscle.

Arm type	Placebo
Investigational medicinal product name	Isotonic saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1ml of sotonic saline was injected into the skin over the masseter muscle.

Number of subjects in period 1	Baseline Granisetron (test-substance)	Baseline Lidocaine (positive control)	Baseline Isotonic saline (placebo)
Started	18	18	18
Completed	18	18	18

Number of subjects in period 1	5min Granisetron (test-substance)	5min Lidocaine (positive control)	5min Isotonic saline (placebo)
Started	18	18	18
Completed	18	18	18

Number of subjects in period 1	20min Granisetron (test-substance)	20min Lidocaine (positive control)	20min Isotonic saline (placebo)
Started	18	18	18
Completed	18	18	18

Number of subjects in period 1	40min Granisetron (test-substance)	40min Lidocaine (positive control)	40min Isotonic saline (placebo)
Started	18	18	18
Completed	18	18	18

Number of subjects in period 1	60min Granisetron (test-substance)	60min Lidocaine (positive control)	60min Isotonic saline (placebo)
Started	18	18	18
Completed	18	18	18

Baseline characteristics

Reporting groups

Reporting group title	Baseline Granisetron (test-substance)
Reporting group description:	
Test was done at baseline before 1ml of granisetron was injected into the skin over the masseter muscle.	
Reporting group title	Baseline Lidocaine (positive control)
Reporting group description:	
Test was done at baseline before 1ml of Lidocaine was injected into the skin over the masseter muscle.	
Reporting group title	Baseline Isotonic saline (placebo)
Reporting group description:	
Test was done at baseline before 1ml of isotonic saline was injected into the skin over the masseter muscle.	
Reporting group title	5min Granisetron (test-substance)
Reporting group description:	
Test was done at 5 min after 1ml of granisetron was injected into the skin over the masseter muscle.	
Reporting group title	5min Lidocaine (positive control)
Reporting group description:	
Test was done at min 5 after 1ml of Lidocaine was injected into the skin over the masseter muscle.	
Reporting group title	5min Isotonic saline (placebo)
Reporting group description:	
Test was done at min 5 after 1ml of isotonic saline was injected into the skin over the masseter muscle.	
Reporting group title	20min Granisetron (test-substance)
Reporting group description:	
Test was done at 20 min after 1ml of granisetron was injected into the skin over the masseter muscle.	
Reporting group title	20min Lidocaine (positive control)
Reporting group description:	
Test was done at min 20 after 1ml of Lidocaine was injected into the skin over the masseter muscle.	
Reporting group title	20min Isotonic saline (placebo)
Reporting group description:	
Test was done at 20 min after 1ml of isotonic saline was injected into the skin over the masseter muscle.	
Reporting group title	40min Granisetron (test-substance)
Reporting group description:	
Test was done at 40 min after 1ml of granisetron was injected into the skin over the masseter muscle.	
Reporting group title	40min Lidocaine (positive control)
Reporting group description:	
Test was done at 40 min after 1ml of Lidocaine was injected into the skin over the masseter muscle.	
Reporting group title	40min Isotonic saline (placebo)
Reporting group description:	
Test was done at 40 min after 1ml of isotonic saline was injected into the skin over the masseter muscle.	
Reporting group title	60min Granisetron (test-substance)
Reporting group description:	
Test was done at 60 min after 1ml of granisetron was injected into the skin over the masseter muscle.	
Reporting group title	60min Lidocaine (positive control)
Reporting group description:	
Test was done at 60 min after 1ml of Lidocaine was injected into the skin over the masseter muscle.	
Reporting group title	60min Isotonic saline (placebo)

Reporting group description:

Test was done at 60 min after 1ml of isotonic saline was injected into the skin over the masseter muscle.

Reporting group values	Baseline Granisetron (test-substance)	Baseline Lidocaine (positive control)	Baseline Isotonic saline (placebo)
Number of subjects	18	18	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)	18	18	18
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	18	18	18

Reporting group values	5min Granisetron (test-substance)	5min Lidocaine (positive control)	5min Isotonic saline (placebo)
Number of subjects	18	18	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)	18	18	18
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	18	18	18

Reporting group values	20min Granisetron (test-substance)	20min Lidocaine (positive control)	20min Isotonic saline (placebo)
Number of subjects	18	18	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)	18	18	18
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	18	18	18

Reporting group values	40min Granisetron (test-substance)	40min Lidocaine (positive control)	40min Isotonic saline (placebo)
Number of subjects	18	18	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)	18	18	18
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	18	18	18

Reporting group values	60min Granisetron (test-substance)	60min Lidocaine (positive control)	60min Isotonic saline (placebo)
Number of subjects	18	18	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)	18	18	18
From 65-84 years	0	0	0
85 years and over	0	0	0

Gender categorical Units: Subjects			
Female	0	0	0
Male	18	18	18

Reporting group values	Total		
Number of subjects	18		
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)	18		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	0		
Male	18		

End points

End points reporting groups

Reporting group title	Baseline Granisetron (test-substance)
Reporting group description: Test was done at baseline before 1ml of granisetron was injected into the skin over the masseter muscle.	
Reporting group title	Baseline Lidocaine (positive control)
Reporting group description: Test was done at baseline before 1ml of Lidocaine was injected into the skin over the masseter muscle.	
Reporting group title	Baseline Isotonic saline (placebo)
Reporting group description: Test was done at baseline before 1ml of isotonic saline was injected into the skin over the masseter muscle.	
Reporting group title	5min Granisetron (test-substance)
Reporting group description: Test was done at 5 min after 1ml of granisetron was injected into the skin over the masseter muscle.	
Reporting group title	5min Lidocaine (positive control)
Reporting group description: Test was done at min 5 after 1ml of Lidocaine was injected into the skin over the masseter muscle.	
Reporting group title	5min Isotonic saline (placebo)
Reporting group description: Test was done at min 5 after 1ml of isotonic saline was injected into the skin over the masseter muscle.	
Reporting group title	20min Granisetron (test-substance)
Reporting group description: Test was done at 20 min after 1ml of granisetron was injected into the skin over the masseter muscle.	
Reporting group title	20min Lidocaine (positive control)
Reporting group description: Test was done at min 20 after 1ml of Lidocaine was injected into the skin over the masseter muscle.	
Reporting group title	20min Isotonic saline (placebo)
Reporting group description: Test was done at 20 min after 1ml of isotonic saline was injected into the skin over the masseter muscle.	
Reporting group title	40min Granisetron (test-substance)
Reporting group description: Test was done at 40 min after 1ml of granisetron was injected into the skin over the masseter muscle.	
Reporting group title	40min Lidocaine (positive control)
Reporting group description: Test was done at 40 min after 1ml of Lidocaine was injected into the skin over the masseter muscle.	
Reporting group title	40min Isotonic saline (placebo)
Reporting group description: Test was done at 40 min after 1ml of isotonic saline was injected into the skin over the masseter muscle.	
Reporting group title	60min Granisetron (test-substance)
Reporting group description: Test was done at 60 min after 1ml of granisetron was injected into the skin over the masseter muscle.	
Reporting group title	60min Lidocaine (positive control)
Reporting group description: Test was done at 60 min after 1ml of Lidocaine was injected into the skin over the masseter muscle.	
Reporting group title	60min Isotonic saline (placebo)

Reporting group description:

Test was done at 60 min after 1ml of isotonic saline was injected into the skin over the masseter muscle.

Primary: Mechanical Detection Threshold Granisetron

End point title	Mechanical Detection Threshold Granisetron[1]

End point description:

The MDT was assessed using calibrated von Frey nylon monofilaments (Anesthesiometer, Somedic Sales AB, Hörby, Sweden) exerting bending forces ranging from 0.026 to 110 g according to the stepwise ascending– descending method in order to find the lowest detectable bending force.

End point type	Primary

End point timeframe:

Mechanical detection threshold was assessed at baseline (before injection) and 5, 20, 40 and 60 min after injection of Granisetron.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Granisetron (test-substance)	5min Granisetron (test-substance)	20min Granisetron (test-substance)	40min Granisetron (test-substance)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	4.156 (± 1.432)	6.206 (± 2.306)	5.856 (± 1.986)	6.172 (± 2.115)

End point values	60min Granisetron (test-substance)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	5.639 (± 2.012)			

Statistical analyses

Statistical analysis title	Difference in MDT Granisetron Baseline-5min

Statistical analysis description:

Difference in Mechanical Detection Threshold from Baseline to 5 min.

Comparison groups	Baseline Granisetron (test-substance) v 5min Granisetron (test-substance)

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	< 0.05
Method	ANOVA

Notes:

[2] - Changes of MDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in MDT Granisetron Baseline-20min

Statistical analysis description:

Difference in Mechanical Detection Threshold from Baseline to 20 min.

Comparison groups	20min Granisetron (test-substance) v Baseline Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	< 0.05
Method	ANOVA

Notes:

[3] - Changes of MDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in MDT Granisetron Baseline-40min

Statistical analysis description:

Difference in Mechanical Detection Threshold from Baseline to 40 min.

Comparison groups	40min Granisetron (test-substance) v Baseline Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	< 0.05
Method	ANOVA

Notes:

[4] - Changes of MDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in MDT Granisetron Baseline-60min

Statistical analysis description:

Difference in Mechanical Detection Threshold from Baseline to 60 min.

Comparison groups	60min Granisetron (test-substance) v Baseline Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	> 0.05
Method	ANOVA

Notes:

[5] - Changes of MDT across times were analyzed using Friedman ANOVA.

Primary: Mechanical Detection Threshold Lidocaine

End point title	Mechanical Detection Threshold Lidocaine[6]

End point description:

The MDT was assessed using calibrated von Frey nylon monofilaments (Anesthesiometer, Somedic Sales AB, Hörby, Sweden) exerting bending forces ranging from 0.026 to 110 g according to the stepwise ascending– descending method in order to find the lowest detectable bending force.

End point type	Primary

End point timeframe:

Mechanical Detection Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Lidocaine.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Lidocaine (positive control)	5min Lidocaine (positive control)	20min Lidocaine (positive control)	40min Lidocaine (positive control)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	4.228 (± 1.150)	9.628 (± 2.417)	6.950 (± 2.630)	6.300 (± 2.552)

End point values	60min Lidocaine (positive control)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	5.978 (± 2.437)			

Statistical analyses

Statistical analysis title	Difference in MDT Lidocaine Baseline-5min

Statistical analysis description:

Difference in Mechanical Detection Threshold from Baseline to 5 min.

Comparison groups	5min Lidocaine (positive control) v Baseline Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	< 0.05
Method	ANOVA

Notes:

[7] - Changes of MDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in MDT Lidocaine Baseline-20min

Statistical analysis description:

Difference in Mechanical Detection Threshold from Baseline to 20 min.

Comparison groups	20min Lidocaine (positive control) v Baseline Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[8]
P-value	< 0.05
Method	ANOVA

Notes:

[8] - Changes of MDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in MDT Lidocaine Baseline-40min

Statistical analysis description:

Difference in Mechanical Detection Threshold from Baseline to 5 min.

Comparison groups	40min Lidocaine (positive control) v Baseline Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[9]
P-value	< 0.05
Method	ANOVA

Notes:

[9] - Changes of CDT, HDT, and MDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in MDT Lidocaine Baseline-60min

Statistical analysis description:

Difference in Mechanical Detection Threshold from Baseline to 60 min.

Comparison groups	60min Lidocaine (positive control) v Baseline Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[10]
P-value	> 0.05
Method	ANOVA

Notes:

[10] - Changes of CDT, HDT, and MDT across times were analyzed using Friedman ANOVA.

Primary: Mechanical Detection Threshold Placebo

End point title	Mechanical Detection Threshold Placebo[11]

End point description:

The MDT was assessed using calibrated von Frey nylon monofilaments (Anesthesiometer, Somedic Sales AB, Hörby, Sweden) exerting bending forces ranging from 0.026 to 110 g according to the stepwise ascending– descending method in order to find the lowest detectable bending force.

End point type	Primary

End point timeframe:

Mechanical Detection Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Isotonic Saline.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Isotonic saline (placebo)	5min Isotonic saline (placebo)	20min Isotonic saline (placebo)	40min Isotonic saline (placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	4.222 (± 1.123)	5.367 (± 1.625)	5.717 (± 1.860)	5.411 (± 1.592)

End point values	60min Isotonic saline (placebo)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	5.267 (± 1.649)			

Statistical analyses

Statistical analysis title	Difference in MDT Isotonic Saline Baseline-5min
Statistical analysis description: Difference in Mechanical Detection Threshold from Baseline to 5 min.	
Comparison groups	Baseline Isotonic saline (placebo) v 5min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[12]
P-value	> 0.05
Method	ANOVA

Notes:

[12] - Changes of MDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in MDT Isotonic Saline Baseline-20min
Statistical analysis description: Difference in Mechanical Detection Threshold from Baseline to 20 min.	
Comparison groups	20min Isotonic saline (placebo) v Baseline Isotonic saline (placebo)

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[13]
P-value	< 0.05
Method	ANOVA

Notes:

[13] - Changes of MDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in MDT Isotonic Saline Baseline-40min

Statistical analysis description:

Difference in Mechanical Detection Threshold from Baseline to 40 min.

Comparison groups	40min Isotonic saline (placebo) v Baseline Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[14]
P-value	< 0.05
Method	ANOVA

Notes:

[14] - Changes of MDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in MDT Isotonic Saline Baseline-60min

Statistical analysis description:

Difference in Mechanical Detection Threshold from Baseline to 60 min

Comparison groups	60min Isotonic saline (placebo) v Baseline Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[15]
P-value	< 0.05
Method	ANOVA

Notes:

[15] - Changes of MDT across times were analyzed using Friedman ANOVA.

Primary: Mechanical Pain Sensitivity Granisetron

End point title	Mechanical Pain Sensitivity Granisetron[16]

End point description:

In order to assess MPS, the von Frey nylon monofilament 19 with a force of 110 g was used.

End point type	Primary

End point timeframe:

Mechanical Pain Sensitivity was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Granisetron.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Granisetron (test-substance)	5min Granisetron (test-substance)	20min Granisetron (test-substance)	40min Granisetron (test-substance)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	39.222 (± 16.275)	30.167 (± 16.176)	31.556 (± 18.234)	34.611 (± 16.832)

End point values	60min Granisetron (test-substance)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	35.500 (± 18.066)			

Statistical analyses

Statistical analysis title	Difference in MPS Granisetron Baseline-5min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 5 min.

Comparison groups	5min Granisetron (test-substance) v Baseline Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[17]
P-value	< 0.05
Method	ANOVA

Notes:

[17] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in MPS.

Statistical analysis title	Difference in MPS Granisetron Baseline-20min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 20 min.

Comparison groups	20min Granisetron (test-substance) v Baseline Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[18]
P-value	< 0.05
Method	ANOVA

Notes:

[18] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in MPS.

Statistical analysis title	Difference in MPS Granisetron Baseline-40min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 40 min.

Comparison groups	40min Granisetron (test-substance) v Baseline Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[19]
P-value	> 0.05
Method	ANOVA

Notes:

[19] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in MPS.

Statistical analysis title	Difference in MPS Granisetron Baseline-60min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 60 min.

Comparison groups	60min Granisetron (test-substance) v Baseline Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	ANOVA

Primary: Mechanical Pain Sensitivity Lidocaine

End point title	Mechanical Pain Sensitivity Lidocaine[20]

End point description:

In order to assess MPS, the von Frey nylon monofilament 19 with a force of 110 g was used.

End point type	Primary

End point timeframe:

Mechanical Pain Sensitivity was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Lidocaine.

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Lidocaine (positive control)	5min Lidocaine (positive control)	20min Lidocaine (positive control)	40min Lidocaine (positive control)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	38.556 (± 14.468)	27.556 (± 19.123)	35.994 (± 16.579)	39.833 (± 17.130)

End point values	60min Lidocaine (positive control)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	38.333 (± 15.718)			

Statistical analyses

Statistical analysis title	Difference in MPS Lidocaine Baseline-5min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 5 min.

Comparison groups	5min Lidocaine (positive control) v Baseline Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[21]
P-value	< 0.05
Method	ANOVA

Notes:

[21] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in MPS.

Statistical analysis title	Difference in MPS Lidocaine Baseline-20min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 20 min.

Comparison groups	20min Lidocaine (positive control) v Baseline Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[22]
P-value	> 0.05
Method	ANOVA

Notes:

[22] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in MPS.

Statistical analysis title	Difference in MPS Lidocaine Baseline-40min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 40 min.

Comparison groups	40min Lidocaine (positive control) v Baseline Lidocaine (positive control)

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[23]
P-value	> 0.05
Method	ANOVA

Notes:

[23] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in MPS.

Statistical analysis title	Difference in MPS Lidocaine Baseline-60min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 60 min.

Comparison groups	60min Lidocaine (positive control) v Baseline Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[24]
P-value	> 0.05
Method	ANOVA

Notes:

[24] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in MPS.

Primary: Mechanical Pain Sensitivity Placebo

End point title	Mechanical Pain Sensitivity Placebo[25]

End point description:

In order to assess MPS, the von Frey nylon monofilament 19 with a force of 110 g was used.

End point type	Primary

End point timeframe:

Mechanical Pain Sensitivity was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Lidocain.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Isotonic saline (placebo)	5min Isotonic saline (placebo)	20min Isotonic saline (placebo)	40min Isotonic saline (placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	36.111 (± 14.552)	28.889 (± 16.743)	32.889 (± 14.336)	34.389 (± 16.881)

End point values	60min Isotonic saline (placebo)			
Subject group type	Reporting group			
Number of subjects analysed	18			

Units: Score				
arithmetic mean (standard deviation)	37.389 (± 16.624)			

Statistical analyses

Statistical analysis title	Difference in MPS Isotonic Saline Baseline-5min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 5 min.

Comparison groups	5min Isotonic saline (placebo) v Baseline Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[26]
P-value	> 0.05
Method	ANOVA

Notes:

[26] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in MPS.

Statistical analysis title	Difference in MPS Isotonic Saline Baseline-20min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 20 min.

Comparison groups	20min Isotonic saline (placebo) v Baseline Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[27]
P-value	> 0.05
Method	ANOVA

Notes:

[27] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in MPS.

Statistical analysis title	Difference in MPS Isotonic Saline Baseline-40min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 40 min.

Comparison groups	40min Isotonic saline (placebo) v Baseline Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[28]
P-value	> 0.05
Method	ANOVA

Notes:

[28] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in MPS.

Statistical analysis title	Difference in MPS Isotonic Saline Baseline-60min

Statistical analysis description:

Difference in Mechanical Pain Sensitivity (MPS) from Baseline to 60 min.

Comparison groups	60min Isotonic saline (placebo) v Baseline Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[29]
P-value	> 0.05
Method	ANOVA

Notes:

[29] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in MPS.

Primary: Cold Detection Threshold Granisetron

End point title	Cold Detection Threshold Granisetron[30]

End point description:

In order to assess the thermal detection threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Cold Detection Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Granisetron.

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Granisetron (test-substance)	5min Granisetron (test-substance)	20min Granisetron (test-substance)	40min Granisetron (test-substance)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	30.021 (± 1.510)	29.342 (± 2.293)	29.426 (± 1.621)	29.513 (± 1.416)

End point values	60min Granisetron (test-substance)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	29.632 (± 1.455)			

Statistical analyses

Statistical analysis title	Difference in CDT Granisetron Baseline-5min

Statistical analysis description:

Difference in Cold Detection Threshold (CDT) from Baseline to 5 min.

Comparison groups	Baseline Granisetron (test-substance) v 5min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[31]
P-value	> 0.05
Method	ANOVA

Notes:

[31] - Changes of CDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in CDT Granisetron Baseline-20min

Statistical analysis description:

Difference in Cold Detection Threshold (CDT) from Baseline to 20 min.

Comparison groups	Baseline Granisetron (test-substance) v 20min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[32]
P-value	> 0.05
Method	ANOVA

Notes:

[32] - Changes of CDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in CDT Granisetron Baseline-40min

Statistical analysis description:

Difference in Cold Detection Threshold (CDT) from Baseline to 40 min.

Comparison groups	Baseline Granisetron (test-substance) v 40min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[33]
P-value	> 0.05
Method	ANOVA

Notes:

[33] - Changes of CDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in CDT Granisetron Baseline-60min

Statistical analysis description:

Difference in Cold Detection Threshold (CDT) from Baseline to 60 min.

Comparison groups	Baseline Granisetron (test-substance) v 60min Granisetron (test-substance)

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[34]
P-value	> 0.05
Method	ANOVA

Notes:

[34] - Changes of CDT across times were analyzed using Friedman ANOVA.

Primary: Cold Detection Threshold Lidocaine

End point title	Cold Detection Threshold Lidocaine[35]

End point description:

In order to assess the thermal detection threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Cold Detection Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Lidocaine.

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Lidocaine (positive control)	5min Lidocaine (positive control)	20min Lidocaine (positive control)	40min Lidocaine (positive control)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	31.576 (± 1.947)	29.103 (± 8.505)	29.896 (± 5.399)	30.868 (± 5.121)

End point values	60min Lidocaine (positive control)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	30.567 (± 6.864)			

Statistical analyses

Statistical analysis title	Difference in CDT Lidocaine Baseline-5min
Statistical analysis description: Difference in Cold Detection Threshold (CDT) from Baseline to 5 min.	
Comparison groups	5min Lidocaine (positive control) v Baseline Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[36]
P-value	> 0.05
Method	ANOVA

Notes:

[36] - Changes of CDT across times were analyzed using Friedman ANOVA

Statistical analysis title	Difference in CDT Lidocaine Baseline-20min
Statistical analysis description: Difference in Cold Detection Threshold (CDT) from Baseline to 20 min.	
Comparison groups	Baseline Lidocaine (positive control) v 20min Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[37]
P-value	> 0.05
Method	ANOVA

Notes:

[37] - Changes of CDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in CDT Lidocaine Baseline-40min
Statistical analysis description: Difference in Cold Detection Threshold (CDT) from Baseline to 40 min.	
Comparison groups	Baseline Lidocaine (positive control) v 40min Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[38]
P-value	> 0.05
Method	ANOVA

Notes:

[38] - Changes of CDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in CDT Lidocaine Baseline-60min
Statistical analysis description: Difference in Cold Detection Threshold (CDT) from Baseline to 60 min.	
Comparison groups	Baseline Lidocaine (positive control) v 60min Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[39]
P-value	> 0.05
Method	ANOVA

Notes:

[39] - Changes of CDT across times were analyzed using Friedman ANOVA.

Primary: Cold Detection Threshold Isotonic saline

End point title	Cold Detection Threshold Isotonic saline[40]

End point description:

In order to assess the thermal detection threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Cold Detection Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Isotonic saline.

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Isotonic saline (placebo)	5min Isotonic saline (placebo)	20min Isotonic saline (placebo)	40min Isotonic saline (placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	30.177 (± 1.309)	28.967 (± 1.979)	28.672 (± 2.253)	28.773 (± 2.614)

End point values	60min Isotonic saline (placebo)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	28.808 (± 2.548)			

Statistical analyses

Statistical analysis title	Difference in CDT Isotonic Saline Baseline-5min

Statistical analysis description:

Difference in Cold Detection Threshold (CDT) from Baseline to 5 min.

Comparison groups	Baseline Isotonic saline (placebo) v 5min Isotonic saline (placebo)

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[41]
P-value	< 0.05
Method	ANOVA

Notes:

[41] - Changes of CDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in CDT Isotonic Saline Baseline-20min

Statistical analysis description:

Difference in Cold Detection Threshold (CDT) from Baseline to 20 min.

Comparison groups	Baseline Isotonic saline (placebo) v 20min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[42]
P-value	> 0.05
Method	ANOVA

Notes:

[42] - Changes of CDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in CDT Isotonic Saline Baseline-40min

Statistical analysis description:

Difference in Cold Detection Threshold (CDT) from Baseline to 40 min.

Comparison groups	Baseline Isotonic saline (placebo) v 40min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[43]
P-value	< 0.05
Method	ANOVA

Notes:

[43] - Changes of CDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in CDT Isotonic Saline Baseline-60min

Statistical analysis description:

Difference in Cold Detection Threshold (CDT) from Baseline to 60 min.

Comparison groups	Baseline Isotonic saline (placebo) v 60min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[44]
P-value	< 0.05
Method	ANOVA

Notes:

[44] - Changes of CDT across times were analyzed using Friedman ANOVA.

Primary: Heat Detection Threshold Granisetron

End point title	Heat Detection Threshold Granisetron[45]

End point description:

In order to assess the thermal detection threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Heat Detection Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Granisetron.

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Granisetron (test-substance)	5min Granisetron (test-substance)	20min Granisetron (test-substance)	40min Granisetron (test-substance)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	33.967 (± 1.230)	35.413 (± 2.707)	34.932 (± 1.633)	35.319 (± 2.447)

End point values	60min Granisetron (test-substance)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	35.154 (± 2.513)			

Statistical analyses

Statistical analysis title	Difference in HDT Granisetron Baseline-5min

Statistical analysis description:

Difference in Heat Detection Threshold (HDT) from Baseline to 5 min.

Comparison groups	Baseline Granisetron (test-substance) v 5min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[46]
P-value	< 0.05
Method	ANOVA

Notes:

[46] - Changes of HDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in HDT Granisetron Baseline-20min

Statistical analysis description:

Difference in Heat Detection Threshold (HDT) from Baseline to 20 min.

Comparison groups	Baseline Granisetron (test-substance) v 20min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[47]
P-value	< 0.05
Method	ANOVA

Notes:

[47] - Changes of HDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in HDT Granisetron Baseline-40min

Statistical analysis description:

Difference in Heat Detection Threshold (HDT) from Baseline to 40 min.

Comparison groups	Baseline Granisetron (test-substance) v 40min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[48]
P-value	< 0.05
Method	ANOVA

Notes:

[48] - Changes of HDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in HDT Granisetron Baseline-60min

Statistical analysis description:

Difference in Heat Detection Threshold (HDT) from Baseline to 60 min.

Comparison groups	Baseline Granisetron (test-substance) v 60min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05 [49]
Method	ANOVA

Notes:

[49] - Changes of HDT across times were analyzed using Friedman ANOVA.

Primary: Heat Detection Threshold Lidocaine

End point title	Heat Detection Threshold Lidocaine[50]

End point description:

In order to assess the thermal detection threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Heat Detection Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Lidocaine.

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Lidocaine (positive control)	5min Lidocaine (positive control)	20min Lidocaine (positive control)	40min Lidocaine (positive control)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	34.379 (± 1.973)	37.723 (± 4.672)	37.262 (± 4.101)	36.160 (± 3.829)

End point values	60min Lidocaine (positive control)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	35.885 (± 3.961)			

Statistical analyses

Statistical analysis title	Difference in HDT Lidocaine Baseline-5min

Statistical analysis description:

Difference in Heat Detection Threshold (HDT) from Baseline to 5 min.

Comparison groups	Baseline Lidocaine (positive control) v 5min Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[51]
P-value	< 0.05
Method	ANOVA

Notes:

[51] - Changes of HDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in HDT Lidocaine Baseline-20min

Statistical analysis description:

Difference in Heat Detection Threshold (HDT) from Baseline to 20 min.

Comparison groups	Baseline Lidocaine (positive control) v 20min Lidocaine

	(positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[52]
P-value	< 0.05
Method	ANOVA

Notes:

[52] - Changes of HDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in HDT Lidocaine Baseline-40min

Statistical analysis description:

Difference in Heat Detection Threshold (HDT) from Baseline to 40 min.

Comparison groups	Baseline Lidocaine (positive control) v 40min Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[53]
P-value	< 0.05
Method	ANOVA

Notes:

[53] - Changes of HDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in HDT Lidocaine Baseline-60min

Statistical analysis description:

Difference in Heat Detection Threshold (HDT) from Baseline to 60 min.

Comparison groups	Baseline Lidocaine (positive control) v 60min Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[54]
P-value	> 0.05
Method	ANOVA

Notes:

[54] - Changes of HDT across times were analyzed using Friedman ANOVA.

Primary: Heat Detection Threshold Isotonic saline

End point title	Heat Detection Threshold Isotonic saline[55]

End point description:

In order to assess the thermal detection threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Heat Detection Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Lidocain Isotonic saline.

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in

order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Isotonic saline (placebo)	5min Isotonic saline (placebo)	20min Isotonic saline (placebo)	40min Isotonic saline (placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	34.576 (± 1.617)	35.145 (± 1.869)	35.518 (± 2.075)	35.434 (± 1.978)

End point values	60min Isotonic saline (placebo)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	35.484 (± 1.728)			

Statistical analyses

Statistical analysis title	Difference in HDT Isotonic Saline Baseline-5min
Statistical analysis description: Difference in Heat Detection Threshold (HDT) from Baseline to 5 min.	
Comparison groups	Baseline Isotonic saline (placebo) v 5min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[56]
P-value	> 0.05
Method	ANOVA

Notes:

[56] - Changes of HDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in HDT Isotonic Saline Baseline20min
Statistical analysis description: Difference in Heat Detection Threshold (HDT) from Baseline to 20 min.	
Comparison groups	Baseline Isotonic saline (placebo) v 20min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[57]
P-value	< 0.05
Method	ANOVA

Notes:

[57] - Changes of HDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in HDT Isotonic Saline Baseline-40min

Statistical analysis description:

Difference in Heat Detection Threshold (HDT) from Baseline to 40 min.

Comparison groups	Baseline Isotonic saline (placebo) v 40min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[58]
P-value	> 0.05
Method	ANOVA

Notes:

[58] - Changes of HDT across times were analyzed using Friedman ANOVA.

Statistical analysis title	Difference in HDT Isotonic Saline Baseline-60min

Statistical analysis description:

Difference in Heat Detection Threshold (HDT) from Baseline to 60 min.

Comparison groups	Baseline Isotonic saline (placebo) v 60min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[59]
P-value	< 0.05
Method	ANOVA

Notes:

[59] - Changes of HDT across times were analyzed using Friedman ANOVA.

Primary: Cold Pain Threshold Garnisetron

End point title	Cold Pain Threshold Garnisetron[60]

End point description:

In order to assess the pain threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Cold Pain Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Granisetron.

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Granisetron (test-substance)	5min Granisetron (test-substance)	20min Granisetron (test-substance)	40min Granisetron (test-substance)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	18.641 (± 7.776)	17.151 (± 9.681)	16.521 (± 8.839)	18.422 (± 7.783)

End point values	60min Granisetron (test-substance)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	16.708 (± 7.869)			

Statistical analyses

Statistical analysis title	Difference in CPT Granisetron Baseline-5min

Statistical analysis description:

Difference in Cold Pain Threshold (CPT) from Baseline to 5 min.

Comparison groups	Baseline Granisetron (test-substance) v 5min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[61]
P-value	> 0.05
Method	ANOVA

Notes:

[61] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.

Statistical analysis title	Difference in CPT Granisetron Baseline-20min

Statistical analysis description:

Difference in Cold Pain Threshold (CPT) from Baseline to 20 min.

Comparison groups	Baseline Granisetron (test-substance) v 20min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[62]
P-value	> 0.05
Method	ANOVA

Notes:

[62] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.

Statistical analysis title	Difference in CPT Granisetron Baseline-40min

Statistical analysis description:

Difference in Cold Pain Threshold (CPT) from Baseline to 40 min.

Comparison groups	Baseline Granisetron (test-substance) v 40min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[63]
P-value	> 0.05
Method	ANOVA

Notes:

[63] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.

Statistical analysis title	Difference in CPT Granisetron Baseline-60min

Statistical analysis description:

Difference in Cold Pain Threshold (CPT) from Baseline to 60 min.

Comparison groups	Baseline Granisetron (test-substance) v 60min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[64]
P-value	> 0.05
Method	ANOVA

Notes:

[64] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.

Primary: Cold Pain Threshold Lidocaine

End point title	Cold Pain Threshold Lidocaine[65]

End point description:

In order to assess the pain threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Cold Pain Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Lidocaine.

Notes:

[65] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Lidocaine (positive control)	5min Lidocaine (positive control)	20min Lidocaine (positive control)	40min Lidocaine (positive control)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	15.582 (±	11.533 (±	13.910 (±	15.953 (±

	9.676)	10.075)	8.743)	9.560)

End point values	60min Lidocaine (positive control)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	15.063 (± 9.501)			

Statistical analyses

Statistical analysis title	Difference in CPT Lidocaine Baseline-5min
Statistical analysis description:	
Difference in Cold Pain Threshold (CPT) from Baseline to 5 min.	
Comparison groups	5min Lidocaine (positive control) v Baseline Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[66]
P-value	> 0.05
Method	ANOVA
Notes:	
[66] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.	

Statistical analysis title	Difference in CPT Lidocaine Baseline-20min
Statistical analysis description:	
Difference in Cold Pain Threshold (CPT) from Baseline to 20 min.	
Comparison groups	20min Lidocaine (positive control) v Baseline Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[67]
P-value	> 0.05
Method	ANOVA
Notes:	
[67] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.	

Statistical analysis title	Difference in CPT Lidocaine Baseline-40min
Statistical analysis description:	
Difference in Cold Pain Threshold (CPT) from Baseline to 40 min.	
Comparison groups	Baseline Lidocaine (positive control) v 40min Lidocaine (positive control)

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[68]
P-value	> 0.05
Method	ANOVA

Notes:

[68] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.

Statistical analysis title	Difference in CPT Lidocaine Baseline-60min

Statistical analysis description:

Difference in Cold Pain Threshold (CPT) from Baseline to 60 min.

Comparison groups	60min Lidocaine (positive control) v Baseline Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[69]
P-value	> 0.05
Method	ANOVA

Notes:

[69] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.

Primary: Cold Pain Threshold Isotonic Saline

End point title	Cold Pain Threshold Isotonic Saline[70]

End point description:

In order to assess the pain threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Cold Detection Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Isotonic Saline.

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Isotonic saline (placebo)	5min Isotonic saline (placebo)	20min Isotonic saline (placebo)	40min Isotonic saline (placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	19.159 (± 9.211)	18.714 (± 11.567)	18.203 (± 10.356)	16.877 (± 11.491)

End point values	60min Isotonic			

	saline (placebo)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	18.029 (± 11.239)			

Statistical analyses

Statistical analysis title	Difference in CPT Isotonic Saline Baseline-5min

Statistical analysis description:

Difference in Cold Pain Threshold (CPT) from Baseline to 5 min.

Comparison groups	Baseline Isotonic saline (placebo) v 5min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[71]
P-value	> 0.05
Method	ANOVA

Notes:

[71] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.

Statistical analysis title	Difference in CPT Isotonic Saline Baseline-20min

Statistical analysis description:

Difference in Cold Pain Threshold (CPT) from Baseline to 20 min.

Comparison groups	Baseline Isotonic saline (placebo) v 20min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[72]
P-value	> 0.05
Method	ANOVA

Notes:

[72] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.

Statistical analysis title	Difference in CPT Isotonic Saline Baseline-40min

Statistical analysis description:

Difference in Cold Pain Threshold (CPT) from Baseline to 40 min.

Comparison groups	Baseline Isotonic saline (placebo) v 40min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[73]
P-value	> 0.05
Method	ANOVA

Notes:

[73] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.

Statistical analysis title	Difference in CPT Isotonic Saline Baseline-60min

Statistical analysis description:

Difference in Cold Pain Threshold (CPT) from Baseline to 60 min.

Comparison groups	60min Isotonic saline (placebo) v Baseline Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[74]
P-value	> 0.05
Method	ANOVA

Notes:

[74] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in CPT.

Primary: Heat Pain Threshold Granisetron

End point title	Heat Pain Threshold Granisetron[75]

End point description:

In order to assess the pain threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Heat Pain Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Granisetron.

Notes:

[75] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Granisetron (test-substance)	5min Granisetron (test-substance)	20min Granisetron (test-substance)	40min Granisetron (test-substance)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	43.617 (± 4.670)	44.746 (± 3.826)	45.190 (± 3.415)	44.766 (± 3.694)

End point values	60min Granisetron (test-substance)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	44.905 (± 3.776)			

Statistical analyses

Statistical analysis title	Difference in HPT Granisetron Baseline-5min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 5 min.

Comparison groups	Baseline Granisetron (test-substance) v 5min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[76]
P-value	> 0.05
Method	ANOVA

Notes:

[76] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Statistical analysis title	Difference in HPT Granisetron Baseline-20min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 20 min.

Comparison groups	Baseline Granisetron (test-substance) v 20min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[77]
P-value	> 0.05
Method	ANOVA

Notes:

[77] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Statistical analysis title	Difference in HPT Granisetron Baseline-40min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 40 min.

Comparison groups	Baseline Granisetron (test-substance) v 40min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[78]
P-value	> 0.05
Method	ANOVA

Notes:

[78] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Statistical analysis title	Difference in HPT Granisetron Baseline-60min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 60 min.

Comparison groups	Baseline Granisetron (test-substance) v 60min Granisetron (test-substance)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[79]
P-value	> 0.05
Method	ANOVA

Notes:

[79] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Primary: Heat Pain Threshold Lidocaine

End point title	Heat Pain Threshold Lidocaine[80]

End point description:

In order to assess the pain threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Heat Pain Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Lidocaine.

Notes:

[80] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Lidocaine (positive control)	5min Lidocaine (positive control)	20min Lidocaine (positive control)	40min Lidocaine (positive control)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	43.555 (± 3.814)	45.378 (± 3.283)	45.197 (± 2.972)	44.187 (± 4.176)

End point values	60min Lidocaine (positive control)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	42.361 (± 9.086)			

Statistical analyses

Statistical analysis title	Difference in HPT Lidocaine Baseline-5min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 5 min.

Comparison groups	Baseline Lidocaine (positive control) v 5min Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[81]
P-value	> 0.05
Method	ANOVA

Notes:

[81] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Statistical analysis title	Difference in HPT Lidocaine Baseline-20min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 20 min.

Comparison groups	Baseline Lidocaine (positive control) v 20min Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[82]
P-value	> 0.05
Method	ANOVA

Notes:

[82] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Statistical analysis title	Difference in HPT Lidocaine Baseline-40min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 40 min.

Comparison groups	Baseline Lidocaine (positive control) v 40min Lidocaine (positive control)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[83]
P-value	> 0.05
Method	ANOVA

Notes:

[83] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Statistical analysis title	Difference in HPT Lidocaine Baseline-60min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 60 min.

Comparison groups	Baseline Lidocaine (positive control) v 60min Lidocaine (positive control)

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[84]
P-value	> 0.05
Method	ANOVA

Notes:

[84] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Primary: Heat Pain Threshold Isotonic Saline

End point title	Heat Pain Threshold Isotonic Saline[85]

End point description:

In order to assess the pain threshold, an electronic thermo-test system was used (CHEPS thermo-test system, Medoc Ltd. Ramat Yishai, Israel). The measurements were done using an advanced thermal stimulator (ATS) with a contact area of 3 × 3 cm that was placed on the skin surface of the masseter. A preset automatic program was used in which the thermal stimulator had a baseline temperature of 32◦C (skin temperature) and a minimum and maximum temperature of 0◦ and 55◦C.

End point type	Primary

End point timeframe:

Heat Pain Threshold was assessed at baseline (before injection) and 5, 20, 40, 60min after injection of Lidocaine.

Notes:

[85] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a cross-over study, but this system cannot accommodate this. Therefore, in order to report the results, we have tried to used workarounds, which means there are only total 3 arms, but in order to report the result as accurately as possible, we have created one arm for each variable. That is why not all arms have been used for each end point.

End point values	Baseline Isotonic saline (placebo)	5min Isotonic saline (placebo)	20min Isotonic saline (placebo)	40min Isotonic saline (placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	18	18
Units: Score				
arithmetic mean (standard deviation)	42.580 (± 4.770)	42.801 (± 4.710)	43.268 (± 4.910)	43.262 (± 4.897)

End point values	60min Isotonic saline (placebo)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Score				
arithmetic mean (standard deviation)	42.931 (± 4.757)			

Statistical analyses

Statistical analysis title	Difference in HPT Isotonic Saline Baseline-5min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 5 min.

Comparison groups	5min Isotonic saline (placebo) v Baseline Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[86]
P-value	> 0.05
Method	ANOVA

Notes:

[86] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Statistical analysis title	Difference in HPT Isotonic Saline Baseline-20min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 20 min.

Comparison groups	Baseline Isotonic saline (placebo) v 20min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[87]
P-value	> 0.05
Method	ANOVA

Notes:

[87] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Statistical analysis title	Difference in HPT Isotonic Saline Baseline-40min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 40 min.

Comparison groups	Baseline Isotonic saline (placebo) v 40min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[88]
P-value	> 0.05
Method	ANOVA

Notes:

[88] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Statistical analysis title	Difference in HPT Isotonic Saline Baseline-60min

Statistical analysis description:

Difference in Heat Pain Threshold (HPT) from Baseline to 60 min.

Comparison groups	Baseline Isotonic saline (placebo) v 60min Isotonic saline (placebo)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[89]
P-value	> 0.05
Method	ANOVA

Notes:

[89] - Two-way ANOVA for repeated measures (RM ANOVA) with time as factor analyzed group differences in HPT.

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: Baseline up to 60 min after injection.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	n/a
Dictionary version	n/a

Frequency threshold for reporting non-serious adverse events: 0 %

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 non-serious adverse events, which we also did not have before when we injected granisetron intramuscularly. The adverse events that exist for granisetron i FASS (mosty constipation and headache) mainly applies to systemic administration with higher doses and not a relatively low single dose that we used.

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

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

There were two researchers performing the examinations and injections. Some of the participants found it difficult to identify the exact transition from non-painful to painful thermal sensation, especially regarding CPT.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32328025