



Clinical trial results:

Local treatment of craniomandibular myofascial pain with the 5-HT3 receptor antagonist granisetron. A randomized and double-blind study.

Summary

EudraCT number	2005-006042-41
Trial protocol	SE
Global end of trial date	31 December 2014

Results information

Result version number	v1 (current)
This version publication date	01 May 2021
First version publication date	01 May 2021

Trial information

Trial identification

Sponsor protocol code	NC3-project
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02230371
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Karolinska Institutet
Sponsor organisation address	17177, Stockholm, Sweden,
Public contact	Department of Dental Medicine, Section for Orofacial Pain and Jaw Function, Karolinska Institutet, Karolinska Institutet, nikolaos.christidis@ki.se
Scientific contact	Department of Dental Medicine, Section for Orofacial Pain and Jaw Function, Karolinska Institutet, Karolinska Institutet, nikolaos.christidis@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	31 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2014
Global end of trial reached?	Yes
Global end of trial date	31 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim for the research project is to investigate if local treatment with granisetron reduces pain in patients with chronic craniomandibular myalgia.

Protection of trial subjects:

The study was approved by the regional ethical review board in Stockholm, Sweden (2006/192-31/4) and by the Medical Products Agency in Uppsala, Sweden (151:2006/7947). Adverse events were systematically collected during the study period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2006
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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was carried out at two centers, the specialist clinics for Orofacial Pain and Jaw Function, Department of Dental Medicine, Karolinska Institutet, Huddinge, Sweden and Clinical Oral Physiology at the Eastman Institute, Stockholm Public Dental Health (Folktandvården Stockholms län AB), Stockholm, Sweden, between May 2006 and December 2014.

Pre-assignment

Screening details:

437 patients were screened, 40 were eligible and included. Inclusion criteria: age ≥ 18 y, diagnosis of myofascial pain, duration of TMD-pain ≥ 3 months, self-assessed average M-TMD pain intensity ≥ 30 mm on a 100-mm VAS during one week prior to examination, pain upon digital palpation of the masseter and/or the temporalis muscles.

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:

The study substances have identical appearance, smell and viscosity so both the patients and examiners were blinded to group assignment. A research assistant assigned the patients to treatment substance in consecutive order according to the randomization list, prepared the syringes and marked them with patient number. A numbered randomization list with the substances in random order in blocks of four was kept hidden to the examiners during the entire study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Granisetron

Arm description:

Granisetron was used as active treatment.

The study comprised seven visits; V1) Screening for study participation and inclusion, V2-V4), Injection of study substances, and V5) Follow-ups at 1-month. Those patients in any group that still reported more than 30 % improvement at the 1-month visit follow-up were scheduled for follow-ups also after 2- (V6) and 6-months (V7).

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

Dosage and administration details:

Granisetron (KYTRIL®; 1 mg/mL, Roche, Stockholm, Sweden) was slowly injected into a maximum of six muscle sites in each patient. The most painful tender-points to palpation of the masticatory muscles were chosen, maximum 3 per muscle. The injected volume into each tender-point was 0.5 mL. Thus the maximum dose of granisetron a patient could receive was 3 mg per treatment.

Arm title	Isotonic saline (placebo)
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Arm description:

Isotonic saline was used as control treatment. The study comprised seven visits; V1) Screening for study participation and inclusion, V2-V4), Injection of study substances, and V5) Follow-ups at 1-month. Those patients in any group that still reported more than 30 % improvement at the 1-month visit follow-up were scheduled for follow-ups also after 2- (V6) and 6-months (V7).

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

Dosage and administration details:

Isotonic saline (NaCl; 0.9 mg/mL, Fresenius Kabi, Uppsala, Sweden) was slowly injected into a maximum of six muscle sites in each patient. The most painful tender-points to palpation of the masticatory muscles were chosen, maximum 3 per muscle. The injected volume into each tender-point was 0.5 mL.

Number of subjects in period 1	Granisetron	Isotonic saline (placebo)
Started	20	20
Completed	20	20

Baseline characteristics

Reporting groups

Reporting group title	Granisetron
Reporting group description:	
Granisetron was used as active treatment. The study comprised seven visits; V1) Screening for study participation and inclusion, V2-V4), Injection of study substances, and V5) Follow-ups at 1-month. Those patients in any group that still reported more than 30 % improvement at the 1-month visit follow-up were scheduled for follow-ups also after 2- (V6) and 6-months (V7).	
Reporting group title	Isotonic saline (placebo)
Reporting group description:	
Isotonic saline was used as control treatment. The study comprised seven visits; V1) Screening for study participation and inclusion, V2-V4), Injection of study substances, and V5) Follow-ups at 1-month. Those patients in any group that still reported more than 30 % improvement at the 1-month visit follow-up were scheduled for follow-ups also after 2- (V6) and 6-months (V7).	

Reporting group values	Granisetron	Isotonic saline (placebo)	Total
Number of subjects	20	20	40
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)	20	20	40
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	38.3	39.1	
standard deviation	± 15.1	± 16.1	-
Gender categorical			
Units: Subjects			
Female	18	19	37
Male	2	1	3
Physical functioning			
Distribution of physical functioning assessed with the Graded Chronic Pain Scale (GCPS).			
Units: Subjects			
GCPS Grade 0	5	12	17
GCPS Grade I	4	1	5
GCPS Grade II	9	4	13
GCPS Grade III	0	1	1
GCPS Grade IV	1	1	2
Missing value	1	1	2

Pain intensity			
Weekly pain intensity (VAS; 0–100 mm). Reported as median (IQR).			
Units: Score			
median	52	57	
standard deviation	± 29	± 24	-
Limitation in jaw function			
Limitation in jaw function assessed with the Jaw Disability Checklist (JDC). Reported as median (IQR).			
Units: Score (0-12)			
median	3	2	
standard deviation	± 5	± 4	-
MWO without pain			
Maximum voluntary mouth opening capacity (MVO) without pain.			
Units: mm			
arithmetic mean	41.1	44.0	
standard deviation	± 9.3	± 10.9	-
MWO with pain			
Maximum voluntary mouth opening capacity (MVO) with pain.			
Units: mm			
arithmetic mean	49.7	52.8	
standard deviation	± 7.5	± 10.0	-

End points

End points reporting groups

Reporting group title	Granisetron
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Reporting group description:

Granisetron was used as active treatment.

The study comprised seven visits; V1) Screening for study participation and inclusion, V2-V4), Injection of study substances, and V5) Follow-ups at 1-month. Those patients in any group that still reported more than 30 % improvement at the 1-month visit follow-up were scheduled for follow-ups also after 2- (V6) and 6-months (V7).

Reporting group title	Isotonic saline (placebo)
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Reporting group description:

Isotonic saline was used as control treatment. The study comprised seven visits; V1) Screening for study participation and inclusion, V2-V4), Injection of study substances, and V5) Follow-ups at 1-month.

Those patients in any group that still reported more than 30 % improvement at the 1-month visit follow-up were scheduled for follow-ups also after 2- (V6) and 6-months (V7).

Primary: Pain intensity at 1, 2, 6 months

End point title	Pain intensity at 1, 2, 6 months
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End point description:

Weekly pain intensity (VAS; 0–100 mm).

Reported as median (IQR).

End point type	Primary
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End point timeframe:

1, 2 and 6 months after repeated tender-point injections with Granisetron (active substance) or Isotonic saline (placebo).

End point values	Granisetron	Isotonic saline (placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Score				
median (standard deviation)				
1 month	29 (± 41)	29 (± 40)		
2 months	32 (± 30)	36 (± 25)		
6 months	24 (± 35)	34 (± 31)		

Statistical analyses

Statistical analysis title	Difference Pain intensity 1 month
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Statistical analysis description:

Difference in pain intensity at 1 month between Granisetron and placebo.

Comparison groups	Granisetron v Isotonic saline (placebo)
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Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Difference Pain intensity 2 months
Statistical analysis description: Difference in pain intensity at 2 months between Granisetron and placebo.	
Comparison groups	Granisetron v Isotonic saline (placebo)
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.009
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Difference Pain intensity 6 months
Statistical analysis description: Difference in pain intensity at 2 months between Granisetron and placebo.	
Comparison groups	Granisetron v Isotonic saline (placebo)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	Wilcoxon (Mann-Whitney)

Secondary: Limitation in jaw function at 1, 2, 6 months

End point title	Limitation in jaw function at 1, 2, 6 months
End point description: Limitation in jaw function assessed with the Jaw Disability Checklist (JDC). Reported as median (IQR).	
End point type	Secondary
End point timeframe: 1, 2 and 6 months after repeated tender-point injections with Granisetron (active substance) or Isotonic saline (placebo).	

End point values	Granisetron	Isotonic saline (placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Score				
median (standard deviation)				
1 month	3 (± 5)	2 (± 4.5)		
2 months	3 (± 4)	2 (± 5.5)		
6 months	3 (± 5)	1 (± 3.5)		

Statistical analyses

Statistical analysis title	Difference Limitation in jaw function 1,2,6months
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Statistical analysis description:

Difference in limitation in jaw function at 1, 2 and 6 months between Granisetron and placebo.

Comparison groups	Isotonic saline (placebo) v Granisetron
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: MWO without pain at 1, 2, 6 months

End point title	MWO without pain at 1, 2, 6 months
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End point description:

Maximum voluntary mouth opening capacity (MVO) without pain.

End point type	Secondary
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End point timeframe:

1, 2 and 6 months after repeated tender-point injections with Granisetron (active substance) or Isotonic saline (placebo).

End point values	Granisetron	Isotonic saline (placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mm				
arithmetic mean (standard deviation)				
1 month	42.9 (± 9.3)	47.6 (± 9.4)		
2 months	43.3 (± 9.4)	46.9 (± 9.4)		
6 months	47.2 (± 10.8)	46.1 (± 6.2)		

Statistical analyses

Statistical analysis title	Difference MWO without pain 1, 2, 6 months
Statistical analysis description: Difference in MWO without pain at 1, 2 and 6 months between Granisetron and placebo.	
Comparison groups	Granisetron v Isotonic saline (placebo)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: MWO with pain at 1, 2, 6 months

End point title	MWO with pain at 1, 2, 6 months
End point description: Maximum voluntary mouth opening capacity (MVO) with pain.	
End point type	Secondary
End point timeframe: 1, 2 and 6 months after repeated tender-point injections with Granisetron (active substance) or Isotonic saline (placebo).	

End point values	Granisetron	Isotonic saline (placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Score (0-12)				
arithmetic mean (standard deviation)				
1 month	47.9 (± 8.2)	52.8 (± 9.5)		
2 months	49.2 (± 7.5)	51.3 (± 9.8)		
6 months	49.3 (± 10.5)	50.4 (± 7.5)		

Statistical analyses

Statistical analysis title	Difference MWO with pain 1, 2, 6 months
Statistical analysis description: Difference in MWO with pain at 1, 2 and 6 months between Granisetron and placebo.	
Comparison groups	Granisetron v Isotonic saline (placebo)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Physical functioning at 1 month

End point title	Physical functioning at 1 month
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End point description:

Distribution of physical functioning assessed with the Graded Chronic Pain Scale (GCPS).

End point type	Secondary
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End point timeframe:

1 month after repeated tender-point injections with Granisetron (active substance) or Isotonic saline (placebo).

End point values	Granisetron	Isotonic saline (placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Distribution				
Grade 0	8	11		
Grade I	6	1		
Grade II	4	2		
Grade III	1	3		
Grade IV	1	0		
Missing value	0	3		

Statistical analyses

Statistical analysis title	Difference Physical functioning 1 month
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Statistical analysis description:

Difference in Physical functioning at 1 month between Granisetron and placebo.

Comparison groups	Granisetron v Isotonic saline (placebo)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Physical functioning at 2 months

End point title	Physical functioning at 2 months
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End point description:

Distribution of physical functioning assessed with the Graded Chronic Pain Scale (GCPS).

End point type	Secondary
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End point timeframe:

2 months after repeated tender-point injections with Granisetron (active substance) or Isotonic saline

(placebo).

End point values	Granisetron	Isotonic saline (placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Distribution				
Grade 0	7	6		
Grade I	1	1		
Grade II	3	1		
Grade III	3	0		
Grade IV	1	0		
Missing value	5	12		

Statistical analyses

Statistical analysis title	Difference Physical functioning 2 months
Statistical analysis description: Difference in Physical functioning at 2 months between Granisetron and placebo.	
Comparison groups	Granisetron v Isotonic saline (placebo)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Physical functioning at 6 months

End point title	Physical functioning at 6 months
End point description: Distribution of physical functioning assessed with the Graded Chronic Pain Scale (GCPS).	
End point type	Secondary
End point timeframe: 6 months after repeated tender-point injections with Granisetron (active substance) or Isotonic saline (placebo).	

End point values	Granisetron	Isotonic saline (placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Distribution				
Grade 0	6	2		
Grade I	1	2		

Grade II	1	1		
Grade III	2	0		
Grade IV	0	0		
Missing value	10	15		

Statistical analyses

Statistical analysis title	Difference Physical functioning at 6 months
Statistical analysis description:	
Difference in Physical functioning at 6 months between Granisetron and placebo.	
Comparison groups	Granisetron v Isotonic saline (placebo)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The patients were asked to list any adverse events during the week following each injection.

Adverse event reporting additional description:

If any adverse event occurred the patients were asked to describe the event and to grade it as mild, moderate or severe. Only mild and short-lasting adverse events were reported after the first injections and no specific dictionary or frequency threshold was used.

Assessment type	Systematic
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Dictionary used

Dictionary name	No specific was used
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Dictionary version	n/a
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Reporting groups

Reporting group title	Granisetron and control
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Reporting group description: -

Serious adverse events	Granisetron and control		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Granisetron and control		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 40 (10.00%)		
Gastrointestinal disorders			
Nausea, constipation, dizziness, hematoma and itching	Additional description: 4 patients in both groups reported mild, short lasting adverse events, such as nausea, constipation, dizziness, hematoma and itching after the first injection of substance. These adverse events did not occur after the second and third injections.		
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		

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.

The results are robust but a limited number of patients participated. The generalizability of the findings should also be investigated in other chronic pain disorders both local and generalized, such as work-related trapezius myalgia or fibromyalgi.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26634569>