Clinical trial results:
A pilot, double-blind, randomized, placebo-controlled, dose finding, proof of concept study to evaluate efficacy, safety and tolerability of self- administered subcutaneous diclofenac sodium 25-50-75mg/1ml in the treatment of an acute migraine attack with headache.

Summary

EudraCT number	2017-004828-29
Trial protocol	IT
Global end of trial date	22 November 2019

Results information

Result version number	v1 (current)
This version publication date	20 April 2022
First version publication date	20 April 2022

Trial information

Trial identification

Sponsor protocol code	17I-DCsc09

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	IBSA, Institut Biochimique S.A
Sponsor organisation address	Via del Piano, Pambio-Noranco, Switzerland, 6915
Public contact	Servizio Informazione sulla Sperime, Pharmaceutical Development and Services srl, 0041 583601000, rd@ibsa.ch
Scientific contact	Servizio Informazione sulla Sperime, Pharmaceutical Development and Services srl, 0039 0557224179, rd@ibsa.ch

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of diclofenac sodium administered subcutaneously at three different doses (25-50-75 mg/1ml) in comparison to placebo in the treatment of an acute migraine attack with headache.

Protection of trial subjects:

Adult out-patients with a diagnosis of migraine, with or without aura. The treatment was self-administered at home at the occurrence of the migraine attack. Patients were allowed to take as a rescue medication (2 hours after the injection of the IMP/placebo) their usual attack medicine or drugs taken for the migraine-associated symptoms (i.e., nausea and vomit).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2018
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	Italy: 122
Worldwide total number of subjects	122
EEA total number of subjects	122

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)	121
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study conducted in 9 investigational study sites in Italy. First patient enrolled: 20 September 2018; Last patient completed: 22 November 2019

Pre-assignment

Screening details:

21 days max of screening period. A total of 139 patients were screened and 129 attended Visit 1 (baseline/randomization visit), while 9 patients were screening failures and 1 voluntary withdrew from the study. A total of 128 patients were randomised to the assigned treatment group (one more patient was a screening failure).

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The Placebo solution was indistinguishable from the IMPs. It was contained in a prefilled syringe identical to the IMPs prefilled syringes

Arms

Are arms mutually exclusive?	Yes
Arm title	Diclofenac 25 mg/ml

Arm description:

1 ml single subcutaneous injection of diclofenac sodium 25 mg

Arm type	Experimental
Investigational medicinal product name	Diclofenac sodium 25mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

SC injection self-administered at home by the patients at the occurrence of the migraine attack

Arm title	Diclofenac 50 mg/ml

Arm description:

1 ml single subcutaneous injection of diclofenac sodium 50 mg

Arm type	Experimental
Investigational medicinal product name	Diclofenac sodium 50 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

SC injection self-administered at home by the patients at the occurrence of the migraine attack

Arm title	Diclofenac 75 mg/ml

Arm description:	
1 ml single subcutaneous injection of diclofenac sodium 75 mg	
Arm type	Experimental
Investigational medicinal product name	Diclofenac sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
SC injection self-administered at home by the patients at the occurrence of the migraine attack	

Arm title	Placebo
Arm description:	
1 ml single subcutaneous injection of NaCl 0,9%	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
SC injection self-administered at home by the patients at the occurrence of the migraine attack. Placebo indistinguishable from IMPs	

Number of subjects in period 1	Diclofenac 25 mg/ml	Diclofenac 50 mg/ml	Diclofenac 75 mg/ml
Started	31	30	30
Completed	31	30	30

Number of subjects in period 1	Placebo
Started	31
Completed	31

Baseline characteristics

Reporting groups	
Reporting group title	Diclofenac 25 mg/ml
Reporting group description:	
1 ml single subcutaneous injection of diclofenac sodium 25 mg	
Reporting group title	Diclofenac 50 mg/ml
Reporting group description:	
1 ml single subcutaneous injection of diclofenac sodium 50 mg	
Reporting group title	Diclofenac 75 mg/ml
Reporting group description:	
1 ml single subcutaneous injection of diclofenac sodium 75 mg	
Reporting group title	Placebo
Reporting group description:	
1 ml single subcutaneous injection of NaCl 0,9%	

Reporting group values	Diclofenac 25 mg/ml	Diclofenac 50 mg/ml	Diclofenac 75 mg/ml
Number of subjects	31	30	30
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)	31	30	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	40.10	38.80	41.93
standard deviation	± 11.36	± 12.93	± 10.43
Gender categorical Units: Subjects			
Female	26	24	28
Male	5	6	2

Reporting group values	Placebo	Total	
Number of subjects	31	122	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	

Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	30	121	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	43.26		
standard deviation	± 10.72	-	
Gender categorical			
Units: Subjects			
Female	26	104	
Male	5	18	

End points

End points reporting groups	
Reporting group title	Diclofenac 25 mg/ml
Reporting group description:	
1 ml single subcutaneous injection of diclofenac sodium 25 mg	
Reporting group title	Diclofenac 50 mg/ml
Reporting group description:	
1 ml single subcutaneous injection of diclofenac sodium 50 mg	
Reporting group title	Diclofenac 75 mg/ml
Reporting group description:	
1 ml single subcutaneous injection of diclofenac sodium 75 mg	
Reporting group title	Placebo
Reporting group description:	
1 ml single subcutaneous injection of NaCl 0,9%	

Primary: percentage of patients pain-free at 2 hours after the study drug injection	
End point title	percentage of patients pain-free at 2 hours after the study drug injection
End point description:	
number and percentage of patients pain-free at 2 hours after the study drug injection in the ITT population.	
End point type	Primary
End point timeframe:	
Baseline-2 hours post treatment	

End point values	Diclofenac 25 mg/ml	Diclofenac 50 mg/ml	Diclofenac 75 mg/ml	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	30	30	31
Units: % of patients	9	14	10	5

Statistical analyses

Statistical analysis title	primary efficacy endpoint
Statistical analysis description:	
number and percentage of patients pain-free at 2 hours after the study drug injection in the ITT population	
Comparison groups	Diclofenac 25 mg/ml v Diclofenac 50 mg/ml v Diclofenac 75 mg/ml v Placebo

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05 [2]
Method	Chi-squared

Notes:

[1] - The primary efficacy endpoint, defined as proportion of subjects completely pain free (pain score= zero) at 2 hours after the study drug injection, will be compared between treatment groups (active groups versus placebo) by means of Chi-Square Test.
[2] - Diclofenac 25mg/ml vs. placebo p= 0.2244
D50 vs. placebo p= 0.0100
D75 vs. placebo p= 0.1188

Secondary: Percentage of patients with the absence of photophobia at 2 hours after the injection

End point title	Percentage of patients with the absence of photophobia at 2 hours after the injection

End point description:

End point type	Secondary

End point timeframe:

Baseline-2 hours after the injection

End point values	Diclofenac 25 mg/ml	Diclofenac 50 mg/ml	Diclofenac 75 mg/ml	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	30	30	31
Units: % of patients	61	80	73	52

Statistical analyses

Statistical analysis title	absence of photophobia at 2 hours after the injec

Statistical analysis description:

Percentage of subjects with the absence of photophobia at 2 hours after the injection using a binary scale (present or absent) will be compared between treatment groups (active groups versus placebo) using Chi-Square Test;

Comparison groups	Diclofenac 25 mg/ml v Diclofenac 50 mg/ml v Diclofenac 75 mg/ml v Placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [3]
Method	Chi-squared

Notes:

[3] - Diclofenac 25mg/ml vs. placebo p= 0.4422
Diclofenac 50mg/ml vs. placebo 0.0197
Diclofenac 75mg/ml vs. placebo 0.0801

Secondary: Percentage of patients with the absence of phonophobia at 2 hours after

the injection

End point title	Percentage of patients with the absence of phonophobia at 2 hours after the injection

End point description:

End point type	Secondary

End point timeframe:

Baseline-2 hours after the treatment

End point values	Diclofenac 25 mg/ml	Diclofenac 50 mg/ml	Diclofenac 75 mg/ml	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	30	30	31
Units: % of patients	74	80	70	71

Statistical analyses

Statistical analysis title	absence of phonophobia at 2 hours after the injec

Statistical analysis description:

Percentage of subjects with the absence of phonophobia at 2 hours after the injection using a binary scale (present or absent) will be compared between treatment groups (active groups versus placebo) using Chi-Square Test;

Comparison groups	Diclofenac 25 mg/ml v Diclofenac 50 mg/ml v Diclofenac 75 mg/ml v Placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.005 [4]
Method	Chi-squared

Notes:

[4] - Diclofenac 25mg/ml vs. placebo 0.7759
Diclofenac 50mg/ml vs. placebo 0.4128
Diclofenac 75mg/ml vs. placebo 0.9340

Secondary: Percentage of patients with the absence of nausea at 2 hours after the injection

End point title	Percentage of patients with the absence of nausea at 2 hours after the injection

End point description:

End point type	Secondary

End point timeframe:

BAseline-2 hours after the treatment

End point values	Diclofenac 25 mg/ml	Diclofenac 50 mg/ml	Diclofenac 75 mg/ml	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	30	30	31
Units: % of patients	58	87	77	61

Statistical analyses

Statistical analysis title	absence of nausea at 2 hours after the injection

Statistical analysis description:

Percentage of subjects with absence of nausea at 2 hours after the injection using a binary scale (present or absent) will be compared between treatment groups (active groups versus placebo) using Chi-Square Test;

Comparison groups	Diclofenac 25 mg/ml v Diclofenac 50 mg/ml v Diclofenac 75 mg/ml v Placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.005 [5]
Method	Chi-squared

Notes:

[5] - Diclofenac 25mg/ml vs. placebo 0.7957
Diclofenac 50mg/ml vs. placebo 0.0243
Diclofenac 75mg/ml vs. placebo 0.1948

Secondary: Percentage of patients with the absence of vomit at 2 hours after the injection

End point title	Percentage of patients with the absence of vomit at 2 hours after the injection

End point description:

End point type	Secondary

End point timeframe:

Baseline-2 hours after the treatment

End point values	Diclofenac 25 mg/ml	Diclofenac 50 mg/ml	Diclofenac 75 mg/ml	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	30	30	31
Units: % of patients	94	97	97	100

Statistical analyses

Statistical analysis title	Absence of vomit at 2 hours after the injection

Statistical analysis description:

Percentage of subjects with absence of vomit at 2 hours after the injection using a binary scale (present or absent) will be compared between treatment groups (active groups versus placebo) using Chi-Square

Test

Comparison groups	Diclofenac 25 mg/ml v Diclofenac 50 mg/ml v Diclofenac 75 mg/ml v Placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.005 [6]
Method	Chi-squared

Notes:

[6] - Diclofenac 25mg/ml vs. placebo 0.1506
Diclofenac 50mg/ml vs. placebo 0.3054
Diclofenac 75mg/ml vs. placebo 0.3054

Adverse events

Adverse events information	
Timeframe for reporting adverse events: screening-End of study visit	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0
Reporting groups	
Reporting group title	Diclofenac sodium 25mg
Reporting group description: -	
Reporting group title	Diclofenac sodium 50mg
Reporting group description: -	
Reporting group title	Diclofenac sodium 75mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Diclofenac sodium 25mg	Diclofenac sodium 50mg	Diclofenac sodium 75mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Diclofenac sodium 25mg	Diclofenac sodium 50mg	Diclofenac sodium 75mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 31 (58.06%)	16 / 30 (53.33%)	19 / 30 (63.33%)
Nervous system disorders			

dizziness			
subjects affected / exposed	0 / 31 (0.00%)	2 / 30 (6.67%)	3 / 30 (10.00%)
occurrences (all)	0	2	3
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	17 / 31 (54.84%)	11 / 30 (36.67%)	15 / 30 (50.00%)
occurrences (all)	18	13	16
Injection site reaction			
subjects affected / exposed	0 / 31 (0.00%)	2 / 30 (6.67%)	3 / 30 (10.00%)
occurrences (all)	0	2	3
Injection site erithema			
subjects affected / exposed	1 / 31 (3.23%)	3 / 30 (10.00%)	5 / 30 (16.67%)
occurrences (all)	1	3	5
Injection site oedema			
subjects affected / exposed	1 / 31 (3.23%)	0 / 30 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	2

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 31 (16.13%)		
Nervous system disorders			
dizziness			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	6		
Injection site reaction			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Injection site erithema			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Injection site oedema			

subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		

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

None reported