Clinical trial results:
A phase 3 randomised, double blind, multiple dose, parallel group efficacy study of different doses of phenylephrine hydrochloride combined with paracetamol and/or ibuprofen in participants with nasal congestion associated with the common cold.

Summary

EudraCT number	2015-002385-23
Trial protocol	GB
Global end of trial date	23 November 2017

Results information

Result version number	v1 (current)
This version publication date	04 January 2020
First version publication date	04 January 2020
Summary attachment (see zip file)	Clinical study report (MXCF-03 final reg report.docx)

Trial information

Trial identification

Sponsor protocol code	AFT-MXCF-03

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AFT Pharmaceuticals Ltd
Sponsor organisation address	129 Hurstmere Road, Takapuna, Auckland, New Zealand, 0622
Public contact	Ioana Stanescu, AFT Pharmaceuticals Ltd, +64 9488 0232 712, ioana@aftpharm.com
Scientific contact	Ioana Stanescu, AFT Pharmaceuticals Ltd, +64 9488 0232 712, ioana@aftpharm.com

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	10 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 November 2017
Global end of trial reached?	Yes
Global end of trial date	23 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Efficacy Objective:
To evaluate and compare the nasal airways resistance (conductance) of fixed dose combination products containing 500 mg paracetamol and 3 mg phenylephrine hydrochloride (Maxiclear™ PE 3.0) or 500 mg paracetamol, 150 mg ibuprofen and 2.5 mg phenylephrine hydrochloride (Maxigesic® PE 2.5) with that of 12 mg phenylephrine hydrochloride and placebo.
Safety Objective:
To determine and compare the safety and tolerability of all treatment groups

Protection of trial subjects:

The informed consent process, the right to withdraw from the study at any time and the ethics committee review of the study protect the rights and benefits of the study participants.

Background therapy: -

Evidence for comparator:

The relative nasal decongestant efficacy of Maxigesic® PE 2.5 and Maxiclear PE 3.0 compared with phenylephrine 12 mg alone and placebo. The lower doses of phenylephrine hydrochloride in both MaxiclearTM PE 3.0 and Maxigesic® PE 2.5 adjust for the interaction between paracetamol and phenylephrine hydrochloride and returns the phenylephrine exposure to that associated with approved phenylephrine hydrochloride doses (10-12 mg) when given as monotherapy (Atkinson et al., 2015a).

Actual start date of recruitment	15 January 2016
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	United Kingdom: 165
Country: Number of subjects enrolled	New Zealand: 112
Worldwide total number of subjects	277
EEA total number of subjects	165

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)	277
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

165 patients were enrolled and completed the study at the Common Cold and Nasal Research Centre, Cardiff School of Biosciences, Cardiff University, Cardiff CF10 3AX prior to the center's closure. Consequently, another 112 participants were enrolled at the New Zealand based investigational site.

Pre-assignment

Screening details:

There were six screening failures, five from NAR < 0.25 Pa/cm3/sec, and one due to potential for tachycardia.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Double blinding was achieved by the use of matching tablets and capsules packaged into identical blisters and cardboard outer containers. Two placebos were used in this study in a double dummy design. Two white capsules enabled double blinding of the study drugs provided by AFT Pharmaceuticals (Maxigesic® PE 2.5 and MaxiclearTM PE 3.0), and a yellow capsule enabled double blinding of the Sudafed® Blocked Nose capsules.

Arms

Are arms mutually exclusive?	Yes
Arm title	Maxigesic® PE 2.5

Arm description:

Paracetamol 1000 mg + ibuprofen 300 mg + phenylephrine hydrochloride 5 mg (administered as 2 tablets of Maxigesic® PE 2.5) + 1 Placebo Capsule

Arm type	Experimental
Investigational medicinal product name	Maxigesic PE 2.5
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two tablets every 4 hours

Arm title	Maxiclear PE 3.0

Arm description:

Paracetamol 1000 mg + phenylephrine hydrochloride 6 mg /dose (administered as 2 tablets of Maxiclear™ PE 3.0) + 1 Placebo Capsule

Arm type	Experimental
Investigational medicinal product name	Maxiclear PE 3.0
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two tablets every 4 hours

Arm title	Sudafed

Arm description:	
Phenylephrine hydrochloride 12 mg (Sudafed® Blocked Nose – 1 Capsule) + 2 Placebo tablets	
Arm type	Active comparator
Investigational medicinal product name	Sudafed Blocked Nose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
One capsule every 4 hours	
Arm title	Placebo
Arm description:	
Placebo (2 Placebo tablets + 1 Placebo capsule)	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Two tablets and one capsule every 4 hours	

Number of subjects in period 1	Maxigesic® PE 2.5	Maxiclear PE 3.0	Sudafed
Started	76	76	75
Completed	76	76	75

Number of subjects in period 1	Placebo
Started	50
Completed	50

Period 2

Period 2 title	Screening and randomization
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator
Blinding implementation details:	
Double blinding was achieved by the use of matching tablets and capsules packaged into identical blisters and cardboard outer containers. Two placebos were used in this study in a double dummy design. Two white capsules enabled double blinding of the study drugs provided by AFT Pharmaceuticals (Maxigesic® PE 2.5 and MaxiclearTM PE 3.0), and a yellow capsule enabled double blinding of the Sudafed® Blocked Nose capsules.	

Arms

Are arms mutually exclusive?	Yes
Arm title	Maxigesic® PE 2.5

Arm description:

Paracetamol 1000 mg + ibuprofen 300 mg + phenylephrine hydrochloride 5 mg (administered as 2 tablets of Maxigesic® PE 2.5) + 1 Placebo Capsule

Arm type	Experimental
Investigational medicinal product name	Maxigesic PE 2.5
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two tablets every 4 hours

Arm title	Maxiclear PE 3.0

Arm description:

Paracetamol 1000 mg + phenylephrine hydrochloride 6 mg /dose (administered as 2 tablets of Maxiclear™ PE 3.0) + 1 Placebo Capsule

Arm type	Experimental
Investigational medicinal product name	Maxiclear PE 3.0
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two tablets every 4 hours

Arm title	Sudafed

Arm description:

Phenylephrine hydrochloride 12 mg (Sudafed® Blocked Nose – 1 Capsule) + 2 Placebo tablets

Arm type	Active comparator
Investigational medicinal product name	Sudafed Blocked Nose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule every 4 hours

Arm title	Placebo

Arm description:

Placebo (2 Placebo tablets + 1 Placebo capsule)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two tablets and one capsule every 4 hours

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Periods were entered in the wrong order. They can not be reordered without affecting

other completed forms.

Number of subjects in period 2	Maxigesic® PE 2.5	Maxiclear PE 3.0	Sudafed
Started	76	76	75
Completed	76	76	75

Number of subjects in period 2	Placebo
Started	50
Completed	50

Baseline characteristics

Reporting groups	
Reporting group title	Maxigesic® PE 2.5
Reporting group description:	
Paracetamol 1000 mg + ibuprofen 300 mg + phenylephrine hydrochloride 5 mg (administered as 2 tablets of Maxigesic® PE 2.5) + 1 Placebo Capsule	
Reporting group title	Maxiclear PE 3.0
Reporting group description:	
Paracetamol 1000 mg + phenylephrine hydrochloride 6 mg /dose (administered as 2 tablets of Maxiclear™ PE 3.0) + 1 Placebo Capsule	
Reporting group title	Sudafed
Reporting group description:	
Phenylephrine hydrochloride 12 mg (Sudafed® Blocked Nose – 1 Capsule) + 2 Placebo tablets	
Reporting group title	Placebo
Reporting group description:	
Placebo (2 Placebo tablets + 1 Placebo capsule)	

Reporting group values	Maxigesic® PE 2.5	Maxiclear PE 3.0	Sudafed
Number of subjects	76	76	75
Age categorical Units: Subjects			
Adults (18-64 years)	76	76	75
Gender categorical Units: Subjects			
Female	43	45	51
Male	33	31	24

Reporting group values	Placebo	Total	
Number of subjects	50	277	
Age categorical Units: Subjects			
Adults (18-64 years)	50	277	
Gender categorical Units: Subjects			
Female	32	171	
Male	18	106	

End points

End points reporting groups

Reporting group title	Maxigesic® PE 2.5
Reporting group description:	
Paracetamol 1000 mg + ibuprofen 300 mg + phenylephrine hydrochloride 5 mg (administered as 2 tablets of Maxigesic® PE 2.5) + 1 Placebo Capsule	
Reporting group title	Maxiclear PE 3.0
Reporting group description:	
Paracetamol 1000 mg + phenylephrine hydrochloride 6 mg /dose (administered as 2 tablets of Maxiclear™ PE 3.0) + 1 Placebo Capsule	
Reporting group title	Sudafed
Reporting group description:	
Phenylephrine hydrochloride 12 mg (Sudafed® Blocked Nose – 1 Capsule) + 2 Placebo tablets	
Reporting group title	Placebo
Reporting group description:	
Placebo (2 Placebo tablets + 1 Placebo capsule)	
Reporting group title	Maxigesic® PE 2.5
Reporting group description:	
Paracetamol 1000 mg + ibuprofen 300 mg + phenylephrine hydrochloride 5 mg (administered as 2 tablets of Maxigesic® PE 2.5) + 1 Placebo Capsule	
Reporting group title	Maxiclear PE 3.0
Reporting group description:	
Paracetamol 1000 mg + phenylephrine hydrochloride 6 mg /dose (administered as 2 tablets of Maxiclear™ PE 3.0) + 1 Placebo Capsule	
Reporting group title	Sudafed
Reporting group description:	
Phenylephrine hydrochloride 12 mg (Sudafed® Blocked Nose – 1 Capsule) + 2 Placebo tablets	
Reporting group title	Placebo
Reporting group description:	
Placebo (2 Placebo tablets + 1 Placebo capsule)	

Primary: Area Under the Curve of Nasal Airflow Conductance

End point title	Area Under the Curve of Nasal Airflow Conductance
End point description:	
End point type	Primary
End point timeframe:	
0-4 hours after the first does of study medication	

End point values	Maxigesic® PE 2.5	Maxiclear PE 3.0	Sudafed	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	76	75	50
Units: AUC NAC				
arithmetic mean (standard error)	905.3 (± 274.7)	901.4 (± 274)	922.3 (± 273.8)	872 (± 232.4)

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Between-treatment differences were tested by means of a one-way analysis of covariance (ANCOVA) model with treatment as a factor and the corresponding baseline (Hour 0, Day 1) value as a covariate

Comparison groups	Placebo v Sudafed v Maxiclear PE 3.0 v Maxigesic® PE 2.5
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard error of the mean

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1-2 of study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Maxigesic® PE 2.5
Reporting group description: Paracetamol 1000 mg + ibuprofen 300 mg + phenylephrine hydrochloride 5 mg (administered as 2 tablets of Maxigesic® PE 2.5) + 1 Placebo Capsule	
Reporting group title	Maxiclear PE 3.0
Reporting group description: Paracetamol 1000 mg + phenylephrine hydrochloride 6 mg /dose (administered as 2 tablets of Maxiclear™ PE 3.0) + 1 Placebo Capsule	
Reporting group title	Sudafed
Reporting group description: Phenylephrine hydrochloride 12 mg (Sudafed® Blocked Nose – 1 Capsule) + 2 Placebo tablets	
Reporting group title	Placebo
Reporting group description: Placebo (2 Placebo tablets + 1 Placebo capsule)	

Serious adverse events	Maxigesic® PE 2.5	Maxiclear PE 3.0	Sudafed
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	0 / 75 (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 / 50 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Maxigesic® PE 2.5	Maxiclear PE 3.0	Sudafed
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 76 (11.84%)	9 / 76 (11.84%)	4 / 75 (5.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 76 (1.32%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	1 / 76 (1.32%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	1 / 75 (1.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 76 (2.63%)	0 / 76 (0.00%)	1 / 75 (1.33%)
occurrences (all)	2	0	1
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 76 (1.32%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences (all)	1	1	0
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 76 (0.00%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Diarrhea			
subjects affected / exposed	0 / 76 (0.00%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 76 (1.32%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	2 / 76 (2.63%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences (all)	2	0	0
Feces soft			

subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	1 / 75 (1.33%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 76 (0.00%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Nasal discomfort			
subjects affected / exposed	0 / 76 (0.00%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Dry throat			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 76 (0.00%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 76 (1.32%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 76 (1.32%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 76 (1.32%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			

subjects affected / exposed	0 / 76 (0.00%)	2 / 76 (2.63%)	0 / 75 (0.00%)
occurrences (all)	0	2	0
Ear infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 76 (0.00%)	0 / 76 (0.00%)	1 / 75 (1.33%)
occurrences (all)	0	0	1

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 50 (8.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Diarrhea			

subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Feces soft subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Nasal congestion subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Nasal discomfort subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Dry throat subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Cough subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Dry skin subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Psychiatric disorders			

Agitation subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0 0 / 50 (0.00%) 0 0 / 50 (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? Yes

Date	Interruption	Restart date
24 March 2017	Premature closure of the Cardiff Investigational site interrupted the trial and led to the opening of the New Zealand trial site.	07 June 2017

Notes:

Limitations and caveats

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

Participants were required to have a cold in order to participate in the trial. The common cold is self-limiting, with symptoms lasting 7-10 days, peaking on day two or three.

Notes: