Clinical trial results:
Randomized, Double-blind, Placebo-controlled, Crossover Design, Efficacy and Safety Study with PA101 in Patients with Indolent Systemic Mastocytosis

Summary

EudraCT number	2014-004113-85
Trial protocol	NL DE ES IT
Global end of trial date	15 June 2016

Results information

Result version number	v1 (current)
This version publication date	24 October 2020
First version publication date	24 October 2020

Trial information

Trial identification

Sponsor protocol code	PA101-SM-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02478957
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Patara Pharma, Inc.
Sponsor organisation address	11455 El Camino Real, Suite 460, San Diego, United States, CA 92130
Public contact	Project Manager, Patara Pharma, Inc., atutuncu@respivant.com
Scientific contact	Project Manager, Patara Pharma, Inc., atutuncu@respivant.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	15 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy profile of PA101 delivered via a high efficiency nebulizer (eFlow®, PARI) in comparison with placebo following 6 weeks of treatment in subjects with indolent systemic mastocytosis (ISM) who were symptomatic despite using standard treatments.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and its revisions as well as with the valid national laws of the participating countries, with the International Council for Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice. The principal investigator was responsible for ensuring that the clinical study was performed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments.

Background therapy:

Subjects continued taking the same daily doses of pre-randomization H1 and H2 antihistamines as well as the same daily doses of any other allowed medication during the Treatment Periods.

Evidence for comparator:

Oral cromolyn sodium (Nalcrom®) is used in the management of subjects with mastocytosis and food intolerance, given orally at doses up to 200 milligrams (mg) four times daily (QID).

Actual start date of recruitment	26 May 2015
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	Netherlands: 6
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	38
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with ISM were recruited to this Phase 2, 2-cohort, 6-week treatment, 2-period crossover study conducted in 8 study centers in 5 countries. The first subject entered the study on 26 May 2015 and the last subject completed on 15 June 2016.

Pre-assignment

Screening details:

Eligible subjects entered a 14-day Run-in Period to establish symptom scores to determine eligibility using an eDiary. At the Baseline Visit eligibility was confirmed and subjects were randomized in a 2:1 ratio to 1 of 2 treatment cohorts and to 1 of 2 treatment sequences in a 1:1 ratio (2 Treatment Periods with a 4-week washout period).

Period 1

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

Blinding implementation details:

For Cohort 1, study subjects, investigators, study staff and the sponsor were blinded to the randomization scheme until all subjects completed the study and the blind was formally broken for all subjects. In Cohort 2, treatment was open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: PA101 then Placebo

Arm description:

Cohort 1 was randomized, double-blind, and placebo-controlled. Subjects were randomly assigned to PA101 or Placebo for Treatment Period 1, and crossed over to the alternative treatment in Treatment Period 2. There was a 4-week washout period between Treatment Periods.

Arm type	Experimental
Investigational medicinal product name	PA101
Investigational medicinal product code	
Other name	Inhaled cromolyn sodium
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

For double-blind Treatment Period 1, subjects received 40 mg PA101 3 times daily (TID), oral inhalation via eFlow for 6 weeks, followed by a 4-week washout period.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

For double-blind Treatment Period 2, subjects received matching placebo TID, oral inhalation via eFlow for 6 weeks.

Arm title	Cohort 1: Placebo then PA101

Arm description:

Cohort 1 was randomized, double-blind, and placebo-controlled. Subjects were randomly assigned to PA101 or Placebo for Treatment Period 1, and the alternative treatment in Treatment Period 2. There was a 4-week washout period between Treatment Periods.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

For double-blind Treatment Period 1, subjects received matching placebo TID, oral inhalation via eFlow for 6 weeks followed by a 4-week washout period.

Investigational medicinal product name	PA101
Investigational medicinal product code	
Other name	Inhaled cromolyn sodium
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

For double-blind Treatment Period 2, subjects received 40 mg PA101 TID, oral inhalation via eFlow for 6 weeks.

Arm title	Cohort 2: PA101 then Nalcrom®

Arm description:

Cohort 2 was an open-label comparison of PA101 with marketed product, oral cromolyn sodium (Nalcrom®). Subjects were randomly assigned to PA101 or Nalcrom® for Treatment Period 1, and crossed over to the alternative treatment in Treatment Period 2. There was a 4-week washout period between Treatment Periods.

Arm type	Experimental
Investigational medicinal product name	PA101
Investigational medicinal product code	
Other name	Inhaled cromolyn sodium
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

For open-label Treatment Period 1, subjects received 40 mg PA101 TID, oral inhalation via eFlow for 6 weeks, followed by a 4-week washout period.

Investigational medicinal product name	Nalcrom®
Investigational medicinal product code	
Other name	Oral cromolyn sodium
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

For open-label Treatment Period 2, subjects received 200 mg Nalcrom® QID, oral capsule for 6 weeks.

Arm title	Cohort 2: Nalcrom® then PA101

Arm description:

Cohort 2 was an open-label comparison of PA101 with marketed product, oral cromolyn sodium (Nalcrom®). Subjects were randomly assigned to PA101 or Nalcrom® for Treatment Period 1, and crossed over to the alternative treatment in Treatment Period 2. There was a 4-week washout period between each treatment.

Arm type	Active comparator
Investigational medicinal product name	Nalcrom®
Investigational medicinal product code	
Other name	Oral cromolyn sodium
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

For open-label Treatment Period 1, subjects received 200 mg Nalcrom® QID, oral capsule for 6 weeks, followed by a 4-week washout period.

Investigational medicinal product name	PA101
Investigational medicinal product code	
Other name	Inhaled cromolyn sodium
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

For open-label Treatment Period 2, subjects received 40 mg PA101 TID, oral inhalation via eFlow for 6 weeks.

Number of subjects in period 1[1]	Cohort 1: PA101 then Placebo	Cohort 1: Placebo then PA101	Cohort 2: PA101 then Nalcrom®
Started	13	14	7
Completed Treatment Period 1	12	13	7
Started Treatment Period 2	12	13	7
Completed	12	12	6
Not completed	1	2	1
Physician decision	-	1	-
Adverse event, non-fatal	1	-	1
Protocol violation	-	1	-

Number of subjects in period 1[1]	Cohort 2: Nalcrom® then PA101
Started	7
Completed Treatment Period 1	6
Started Treatment Period 2	6
Completed	5
Not completed	2
Physician decision	-
Adverse event, non-fatal	2
Protocol violation	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 42 subjects were enrolled and randomized. One subject included in Cohort 1 was randomized in error as they did not meet all inclusion criteria. This subject did not receive any study medication and was excluded from all analysis sets. Therefore, a total of 27 subjects started Cohort 1 and 14 subjects started Cohort 2.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: PA101 then Placebo
Reporting group description:	
Cohort 1 was randomized, double-blind, and placebo-controlled. Subjects were randomly assigned to PA101 or Placebo for Treatment Period 1, and crossed over to the alternative treatment in Treatment Period 2. There was a 4-week washout period between Treatment Periods.	
Reporting group title	Cohort 1: Placebo then PA101
Reporting group description:	
Cohort 1 was randomized, double-blind, and placebo-controlled. Subjects were randomly assigned to PA101 or Placebo for Treatment Period 1, and the alternative treatment in Treatment Period 2. There was a 4-week washout period between Treatment Periods.	
Reporting group title	Cohort 2: PA101 then Nalcrom®
Reporting group description:	
Cohort 2 was an open-label comparison of PA101 with marketed product, oral cromolyn sodium (Nalcrom®). Subjects were randomly assigned to PA101 or Nalcrom® for Treatment Period 1, and crossed over to the alternative treatment in Treatment Period 2. There was a 4-week washout period between Treatment Periods.	
Reporting group title	Cohort 2: Nalcrom® then PA101
Reporting group description:	
Cohort 2 was an open-label comparison of PA101 with marketed product, oral cromolyn sodium (Nalcrom®). Subjects were randomly assigned to PA101 or Nalcrom® for Treatment Period 1, and crossed over to the alternative treatment in Treatment Period 2. There was a 4-week washout period between each treatment.	

Reporting group values	Cohort 1: PA101 then Placebo	Cohort 1: Placebo then PA101	Cohort 2: PA101 then Nalcrom®
Number of subjects	13	14	7
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	50.4	47.2	41.1
standard deviation	± 10.67	± 12.94	± 16.83
Gender categorical Units: Subjects			
Female	8	11	5
Male	5	3	2

Reporting group values	Cohort 2: Nalcrom® then PA101	Total	
Number of subjects	7	41	

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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	53.4		
standard deviation	± 15.52	-	
Gender categorical Units: Subjects			
Female	5	29	
Male	2	12	

End points

End points reporting groups

Reporting group title	Cohort 1: PA101 then Placebo

Reporting group description:

Cohort 1 was randomized, double-blind, and placebo-controlled. Subjects were randomly assigned to PA101 or Placebo for Treatment Period 1, and crossed over to the alternative treatment in Treatment Period 2. There was a 4-week washout period between Treatment Periods.

Reporting group title	Cohort 1: Placebo then PA101

Reporting group description:

Cohort 1 was randomized, double-blind, and placebo-controlled. Subjects were randomly assigned to PA101 or Placebo for Treatment Period 1, and the alternative treatment in Treatment Period 2. There was a 4-week washout period between Treatment Periods.

Reporting group title	Cohort 2: PA101 then Nalcrom®

Reporting group description:

Cohort 2 was an open-label comparison of PA101 with marketed product, oral cromolyn sodium (Nalcrom®). Subjects were randomly assigned to PA101 or Nalcrom® for Treatment Period 1, and crossed over to the alternative treatment in Treatment Period 2. There was a 4-week washout period between Treatment Periods.

Reporting group title	Cohort 2: Nalcrom® then PA101

Reporting group description:

Cohort 2 was an open-label comparison of PA101 with marketed product, oral cromolyn sodium (Nalcrom®). Subjects were randomly assigned to PA101 or Nalcrom® for Treatment Period 1, and crossed over to the alternative treatment in Treatment Period 2. There was a 4-week washout period between each treatment.

Subject analysis set title	Cohort 1: PA101
Subject analysis set type	Full analysis

Subject analysis set description:

All Cohort 1 subjects who received PA101 in Treatment Periods 1 and 2.

Subject analysis set title	Cohort 1: Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

All Cohort 1 subjects who received placebo in Treatment Periods 1 and 2.

Subject analysis set title	Cohort 2: PA101
Subject analysis set type	Full analysis

Subject analysis set description:

All Cohort 2 subjects who received PA101 in Treatment Periods 1 and 2.

Subject analysis set title	Cohort 2: Nalcrom®
Subject analysis set type	Full analysis

Subject analysis set description:

All Cohort 2 subjects who received Nalcrom® in Treatment Periods 1 and 2.

Primary: Mean Change from Baseline in the Average Daily Modified Mastocytosis Activity of Symptoms (MAS) Plus Severity Score at Week 6

End point title	Mean Change from Baseline in the Average Daily Modified Mastocytosis Activity of Symptoms (MAS) Plus Severity Score at Week 6

End point description:

Subjects used a daily eDiary for the assessment of symptoms using the MAS Plus questionnaire throughout the study. The MAS Plus questionnaire is a 27-item, disease-specific questionnaire designed to measure impact of systemic mastocytosis on overall health, daily life and perceived well-being of subjects across 5 different organ systems/domains: skin (pruritus, whealing, and flushing); gastrointestinal (diarrhea and abdominal pain); central nervous system (headache and difficulty concentrating); musculoskeletal (bone pain) and general system (fatigue). The MAS plus Severity Score was calculated as the total of all 9 symptoms. The maximum daily MAS Plus Severity Score is 90 with higher scores indicating a higher disease activity. The average daily score was calculated using the 14

days pre-treatment for baseline and the last 14 days of treatment for each treatment period.

End point type	Primary

End point timeframe:
Baseline and Week 6.

End point values	Cohort 1: PA101	Cohort 1: Placebo	Cohort 2: PA101	Cohort 2: Nalcrom®
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	26	13	14
Units: Score on a scale				
arithmetic mean (standard deviation)	-3.8 (± 8.41)	-6.8 (± 9.58)	-6.9 (± 12.23)	-4.0 (± 7.16)

Statistical analyses

Statistical analysis title	Treatment Difference: Cohort 1 (PA101 - Placebo)
Comparison groups	Cohort 1: PA101 v Cohort 1: Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2695
Method	Mixed models analysis
Parameter estimate	Least squares (LS) mean difference
Point estimate	2.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.99
upper limit	6.74

Statistical analysis title	Treatment Difference: Cohort 2 (PA101 - Nalcrom®)
Comparison groups	Cohort 2: PA101 v Cohort 2: Nalcrom®
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.542
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	4.71

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were assessed from the Baseline Visit up to Week 6 of each Treatment Period, and at the Safety Follow-up visit within 7 days after the last study treatment.

Adverse event reporting additional description:

Treatment emergent AEs are presented overall for all subjects in both Cohorts 1 and 2 who received PA101.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Overall: PA101

Reporting group description:

All subjects in Cohorts 1 and 2 who received PA101 (40 mg TID, oral inhalation via eFlow for 6 weeks) during Treatment Periods 1 and 2.

Serious adverse events	Overall: PA101		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 39 (2.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Vascular pseudoaneurysm ruptured			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Overall: PA101		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 39 (48.72%)		
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Genital burning sensation			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Gastrointestinal infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2 2 / 39 (5.13%) 2 2 / 39 (5.13%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2015	- Inclusion criterion regarding written informed consent was clarified. - Exclusion criteria were clarified regarding reliable contraception and for subjects under guardianship, trusteeship, or committed to an institution by order of government or judicial authorities or who had a relationship so that they were rendered dependent to the investigator/study center staff or the sponsor. - Examples of conditions that would warrant a termination of the study by the sponsor were added. - Tests for significance testing of the efficacy analyses were updated. - Reference for the Declaration of Helsinki was corrected.
12 August 2015	- It was clarified that subjects needed to have used at least 1 of the given therapies (i.e. H1 and/or H2 antihistamines and/or other antimediator therapy) to be eligible for the study. - A timeframe of 6 weeks for the history of systemic corticosteroid use was added to the exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported