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

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Primary:* 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 patients with indolentsystemic mastocytosis (ISM) who are symptomatic despite...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON41987

Source
ToetsingOnline

Brief title
Disodium Cromoglycate study in ISM patients

Condition

- Haematological disorders NEC

Synonym
Indolent Systemic Mastocytosis

Research involving
Human

Sponsors and support

Primary sponsor: Patara Pharma, LLC
Source(s) of monetary or material Support: Pharmaceutical company: Patara Pharmacueticals LLC;U.S.A

Intervention

Keyword: cromolyn sodium), Disodium Cromoglycate (DSCG, Efficacy and Safety, Indolent Systemic Mastocytosis, Tolerability

Outcome measures

Primary outcome

Efficacy measurements:

Efficacy analyses will be performed for each cohort separately.

* Primary:

o Changes from baseline in total symptom score using the MAS Plus questionnaire

at 6 weeks

Secondary outcome

* Secondary:

o Changes from baseline in each organ system domain in the MAS Plus

questionnaire

o Changes from baseline in each symptom score in the MAS Plus questionnaire

o Change from baseline in quality of life score using the MIQ questionnaire

o Change from baseline in quality of life score using the SF-36 questionnaire

o PGIC score

o Proportion of patients requiring rescue medication

o Proportion of patients who dropped out due to lack of efficacy

o Frequency of rescue medication use

o Change from baseline in mast cell burden (i.e., plasma and urine biomarkers).

Pharmacokinetic measurements:

Pharmacokinetic measurements will be estimated for each cohort.

* Maximum concentration (Cmax)

* Time to maximum concentration (Tmax)

* Terminal elimination half-life (T1/2)

* Area under the plasma concentration-time curve from time = 0 to time of last measurable drug concentration (AUC0-t)

* Area under the plasma concentration-time curve from time = 0 to infinity (AUC0-inf).

Safety measurements:

Safety analyses will be performed for each cohort separately and combined.

* Adverse events

* Changes in vital signs

* Changes in 12-lead ECG

* Changes in clinical laboratory tests (i.e., hematology, biochemistry, and urinalysis

Statistical Measurements:

Efficacy analyses will be performed for each cohort separately. To test for

significant differences between the treatments with respect to the primary and secondary efficacy endpoints, analysis of covariance (ANCOVA) will be used with sequence, treatment (PA101 and placebo or PA101 and Nalcrom), and period as the fixed effects, and patient nested within sequence as a random effect, and the baseline score as the covariate. Based on the model, the difference between the treatments will be estimated along with the 2-sided 95% confidence intervals.

PK parameters and plasma concentrations of cromolyn sodium will be summarized by treatment for each cohort separately and combined. The summary statistics will be presented as the geometric mean, arithmetic mean, arithmetic standard deviation, minimum, median, maximum, and n. For Tmax, geometric statistics will not be presented. For Cohort 2, following logarithmic transformation, Cmax and AUC values will be subjected to an analysis of variance (ANOVA) with sequence, treatment, period as fixed effects and patient nested within sequence as a random effect. For comparison, point estimates and 90% CI for the difference between PA101 and Nalcrom will be constructed using the residual mean square error obtained from the ANOVA. The point and interval estimates will then be back-transformed to give estimates of the ratio of the geometric least squares mean and the corresponding 90% CI.

For safety analyses, cohorts will be summarized separately and combined. The incidence of AEs will be compared between treatment arms. Summary tables and individual patient listings will be provided for all safety measurements, and the results will be presented by treatment. Descriptive statistics will be

used to summarise data where appropriate.

Study description

Background summary

Mast cell activation syndromes (MCB) are becoming increasingly important in adults and Children. Mastocytosis is a disease that is characterized by a pathological increase in the number of mast cells in different tissues (skin, spleen, liver, gastrointestinal tract and bone marrow). There are no curative therapies for mastocytosis, and patients are treated symptomatically.
Inhaled cromolyn sodium is used as an anti-inflammatory agent in the management of allergic asthma in adults and pediatric patients (ie 2 years and older).
This is regularly given by oral inhalation with a universal nebulizer dose to 20 mg four times a day or as an inhaler (ie, dry powder inhaler [DPI], and metered dose inhaler [MDI], (although it is not placed on the market at this time) of dose to 20 mg four times daily.
Oral cromolyn sodium is currently used in the treatment of patients with mastocytosis and food intolerance and four times a day, administered orally in doses up to 200 mg.
Cromolyn sodium has been tested with dose up to 80 mg as a single oral inhalation and to 4 mg intravenously to healthy patients.
Long-term treatment with cromolyn sodium administered through inhalation, oral, intranasal, and ocular have been reported to be safe and tolerated at all patient populations, including pediatric patients and age groups

Study objective

Primary:
* 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 patients with indolent
systemic mastocytosis (ISM) who are symptomatic despite using standard treatments

Secondary:
* To compare the efficacy and safety profile of PA101 to marketed oral cromolyn sodium (open-label
control)
* To assess the safety, tolerability, and pharmacokinetic (PK) profile of PA101

Study design

This is a Phase 2, 2-cohort, multi-center, 6-week treatment, 2-period crossover efficacy and safety study of PA101 in 36 patients with ISM. Cohort 1 is randomized, double-blind and placebo-controlled. Cohort 2 is an open-label comparison of PA101 with a marketed product (i.e., oral cromolyn sodium [Nalcrom®]).
Following the Screening Visit (SV), eligible patients will enter a 14-day (± 2 days) Run-in Period. Patients enrolled in the Run-in Period must:
* Experience symptoms with a severity score of at least 4 for at least 7 out of 14 days during the Run-in Period with at least one qualifying symptom each from at least two organ systems, despite the use of H1 and H2 antihistamines and other anti-mediator therapy (not well-controlled), and
* Currently not be using oral cromolyn sodium.
The symptom scores for determining eligibility will be established during the 14-day (± 2 days) Run-in Period using an electronic daily diary (eDiary). Following the Run-in Period, a Baseline Visit will be performed to confirm eligibility.
The organ systems and the qualifying symptoms listed on the modified Mastocytosis Activity of Symptoms (MAS Plus) questionnaire are: skin (pruritus, whealing, and flushing), gastrointestinal (diarrhea and abdominal pain), central nervous system (headache and difficulty concentrating), musculoskeletal (bone pain), and general system (fatigue).
If patients meet all the eligibility criteria at the Baseline Visit of Period 1, they will be randomly allocated in a 2:1 ratio to one of two treatment cohorts (i.e., Cohorts 1 and 2) and to one of two treatment sequences in a 1:1 ratio on the first day of the Treatment Period (Baseline Visit 1) in accordance with the randomization scheme in Figure 1. Each treatment cohort will include two Treatment Periods of 6 weeks each (42 ± 2 days) in a 2-period crossover design. In Cohort 1 (n=24), patients will receive two inhalation treatments (i.e., 40 mg PA101 and placebo PA101) three times daily(TID) via eFlow for 6 weeks each in a double-blind, 2-period crossover fashion with a 4-week washout period between the treatment periods. In Cohort 2 (n=12), patients will receive oral cromolyn sodium (i.e., Nalcrom capsule) 200 mg QID and inhaled 40 mg PA101 TID via eFlow for 6 weeks each in an open label, 2-period crossover fashion with a 4-week washout period between the treatment periods.
Patients will continue taking the same daily doses of pre-randomization H1 and H2 antihistamines as well as the same daily doses of any other allowed medications during the Treatment Period. H1 antihistamines (additional doses of currently used H1 antihistamine or a different H1 antihistamine not used at the time of study entry) will be allowed as rescue medication during the Treatment Period at the discretion of the Investigator if the clinical symptoms are not controlled with the allocated study treatment. Use of rescue medication will be recorded in the case report form for comparison between treatment arms

Intervention

Patients will be randomized in 2:1 ratio to one of the following two treatment cohorts with 2 treatment periods in each cohort:

Cohort 1 (n=24): Double-blind
* Treatment 1: 40 mg PA101 TID, oral inhalation via eFlow for 6 weeks
* Treatment 2: Placebo PA101 TID, oral inhalation via eFlow for 6 weeks
Cohort 2 (n=12): Open-label
* Treatment 1: 40 mg PA101 TID, oral inhalation via eFlow for 6 weeks
* Treatment 2: Nalcrom® 200 mg QID, oral capsule for 6 weeks
Eligible patients in each cohort will be randomly allocated to one of two treatment sequences in a 1:1 ratio at the Baseline Visit of Period 1. There will be a washout period of 28 ± 4 days between two treatment periods in each treatment cohort.
Study patients will receive the allocated inhalation study treatment (PA101 and Placebo PA101) three times daily: 8:00 am, 2:00 pm and 8:00 pm (± 1 hour).
Patients will receive the oral study treatment (Nalcrom capsule) four times daily: 7:00 am, 12:00 pm, 5:00 pm, and 10:00 pm (± 1 hour).
During select Treatment Visits (i.e., V1, V3 and V4), a subset of patients (approximately 6 patients per cohort) will receive the assigned morning treatment in the clinic and will remain in the clinic up to 6 hours for serial PK blood draws.
Study patients will be asked to record symptom scores daily in an electronic eDiary during the Run-in Period, the Treatment Periods and the Washout Period.
The quality-of-life assessments will be performed at the Baseline Visit, and at pre-specified treatment visits in the clinic during each Treatment Period.

Study burden and risks

It is possible that some of the topics in the questionnaires may be sensitive or embarrassing. The investigators will ensure that the consultations take place in a private environment and will make every effort to make the trial subject/parent/caregiver as relaxed and comfortable as possible.

What is the potential for benefit to trial subjects?
There is no guaranteed benefit to the trial subjects from taking part in this study. If treatment works it may help to control the disease. The investigator will assess the balance of risks and benefits of continuing to participate in the study. Even if the research participants do not benefit personally from the study, the information gained may facilitate the development of better treatment for patients with Indolent systemic Mstocytosis.
The investigator will discuss alternative treatment options with the subject for subject's future care

Contacts

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria:
1. Male or female patients 18-75 years of age, inclusive
2.Diagnosed with indolent systemic mastocytosis (ISM) according to the WHO criteria and the consensus proposal (2001)
3. Experiencing at least one qualifying symptom in at least two organ systems during the 3 months preceding the Screening Visit, despite the use of H1 and/or H2 antihistamines and/or other anti-mediator therapy
4. Experiencing symptoms with a severity score of at least 4 for at least 7 out of 14 days during the Run-in Period with at least one qualifying symptom each from at least two organ systems, despite the use of H1 and/or H2 antihistamines and/or other anti-mediator therapy.
5. Willing and able to use an eDiary device daily for the duration of the study
6. Completed at least 5 eDiary reports during each of two consecutive weeks of the Run-in Period
7. Patients must digitally accept the licensing agreement in the eDiary software
8. Willingness and ability to provide written informed consent prior to any study procedures performed

Exclusion criteria

Exclusion criteria:
1. Advanced systemic mastocytosis (i.e., aggressive systemic mastocytosis [ASM], mast cell leukemia [MCL], or systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease [SM-AHNMD])
2. Current or recent history of clinically significant cardiovascular, hematological, renal, neurologic, hepatic, endocrine, psychiatric, malignant, or other illnesses that could put the patient at risk or compromise the quality of the study data as determined by the Investigator
3. Use of oral cromolyn sodium within 6 weeks of the Screening Visit
4. History of systemic corticosteroid use within 6 weeks, or immunosuppressive, or anti-IgE monoclonal antibody therapy (e.g., omalizumab) within 6 months of the Screening Visit
5. History of anaphylaxis requiring systemic treatment (i.e., corticosteroid or epinephrine) within 12 months of the Screening Visit
6. An upper or lower respiratory tract infection within 4 weeks of the Screening Visit
7. History of malignancy within the last 5 years, except basal cell carcinoma or cervix carcinoma in situ
8. Major surgery within 6 months of the Screening Visit
9. History of excessive use or abuse of alcohol (i.e., more than 3 units per day, or more than 21 units per week) within 12 months of the Screening Visit
10. History of abusing legal drugs or use of illegal drugs or substances within 12 months of the Screening Visit
11. Females who are pregnant or breastfeeding, or if of child-bearing potential unwilling to practice acceptable means of birth control or abstinence during the study; females of child-bearing potential must use one reliable method of contraception (i.e., Pearl Index of less than 1%)
12. Participation in any other investigational drug study within 4 weeks of the Screening Visit
13. History of hypersensitivity or intolerance to aerosol medications or cromolyn sodium
14. Patients under guardianship, trusteeship, or committed to an institution by order of government or judicial authorities
15. Patients who have a relationship as such that they are rendered dependent to the investigator/study site staff, or the sponsor.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-07-2015
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	eFlow®
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	PA101
Generic name:	Cromolyn soduim

Ethics review

Approved WMO Date:	04-12-2014
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	16-04-2015
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	16-12-2015
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-004113-85-NL
CCMO	NL51277.094.14