A Phase 2, Randomized, Double-Blind, Placebo Controlled, Study to Evaluate Multiple Doses of AK001 in Patients With Moderate to Severe Nasal Polyposis

Published: 26-04-2016
Last updated: 16-04-2024

Primary objective:To evaluate the effect of each of 2 doses of AK001 separately in combination with an INS versus the INS alone on the reduction in size of nasal polyps as evaluated by the change from Baseline to Week 12 after the start of treatment...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON42893

Source
ToetsingOnline

Brief title
AK001-002

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Nasal polyposis; nasal polyps

Research involving
Human

Sponsors and support

Primary sponsor: MediServ

Source(s) of monetary or material Support: Allakos Inc

Intervention

Keyword: Nasal, Polyposis

Outcome measures

Primary outcome

The following specific efficacy evaluations will be conducted in all patients:

* TPS of nasal endoscopy (blinded centralized evaluation)

* Size of polyps as evaluated by Lund-Mackay score at selected sites by CT scan

* Nasal airway patency as evaluated by PNIF

* Ability to smell (UPSIT)

* SNOT-22 (patient-reported symptoms)

* VASs (patient-reported symptoms)

* SF-36 (quality of life)

* Blood eosinophil and basophil absolute counts

* Potentially explore markers of MCs and eosinophils and inflammatory response

in blood

The following specific additional efficacy evaluations will be conducted in

asthmatic patients:

* TPS of nasal endoscopy (blinded centralized evaluation)

* Pulmonary function (FEV1, FVC, and FEF) assessed using spirometry

* ACT

* Use of asthma rescue therapy

Secondary outcome

The safety and tolerability of each of 2 doses of AK001 separately as well as

combined will be assessed by determining the incidence, relationship to study drug, and severity of TEAEs, withdrawals due to AEs, and changes in vital signs, laboratory test (including anti-drug antibody [ADA]) findings, concomitant medication use, and physical examination (PE) findings. Safety results in patients dosed with each of 2 doses of AK001 separately as well as combined will be compared with those in patients dosed with placebo.

Study description

Background summary

Nasal polyps are benign edematous masses that can cause nasal obstruction, rhinorrhea, facial pressure, postnasal drip, and loss of smell. It is estimated that nasal polyps affect 1% to 4% of the general population with a 2:1 male to female preponderance. The incidence increases with age, with peak incidence between 40 and 60 years of age. Although the etiology of nasal polyposis (recurrent, multiple polyps) is unknown, various comorbidities, such as chronic inflammation of the mucous membranes in the nose and paranasal sinuses, allergic rhinitis, atopy, and asthma have been proposed as factors in the genesis of nasal polyposis.
Phenotypically, chronic rhinosinusitis (CRS) can be classified as either without nasal polyposis (CRSsNP) or with nasal polyposis (CRSwNP), which comprises the majority of cases of nasal polyposis. The more common CRSwNP is often characterized by eosinophilic inflammation with high levels of eosinophil cationic protein; interleukins (IL)-4, IL-5, and IL-13; and tissue immunoglobulin E (IgE).
Treatment options for nasal polyposis range from topical and/or systemic corticosteroids to functional endoscopic sinus surgery. Patients with CRSwNP and comorbid asthma, in particular, have a poor therapeutic response and high polyp recurrence rate, and their diseases are more difficult to treat. Both diseases have an adverse effect on quality of life and confer a large economic burden.
AK001 is a humanized immunoglobulin G4 (IgG4) monoclonal antibody directed against Siglec-8, a member of the CD33 related family of sialic acid-binding, immunoglobulin like lectins (siglecs). No close homolog has been found in other animal or primate species apart from great apes and baboons. Consequently, AK001 has been studied in Siglec-8 humanized and transgenic mouse models and with human blood and tissue cells. Siglec-8 has a restricted tissue distribution and is expressed selectively on the surface of mature eosinophils,

mast cells (MCs), and at lower levels on basophils but not in early precursors of these cell populations or other blood cells. Crosslinking of Siglec-8 by AK001 can induce apoptosis of eosinophils previously activated by certain cytokines. The antibody does not induce apoptosis in MCs, but inhibits histamine release and de novo synthesis of prostaglandin D2 (PGD2) induced by IgE receptor activation.
High levels of eosinophils and of MCs (up to 8% of isolated cells) are evident in nasal polyps. Mast cells and eosinophils isolated from nasal polyps have been shown by flow cytometry to express surface Siglec-8.
By reducing activated eosinophils and blocking mast-cell histamine and PGD2 release, AK001 may be useful in the treatment of patients with moderate to severe chronic nasal polyposis with predominant eosinophilic and MC inflammation and whose symptoms are resistant to treatment with intranasal steroids (INSs).

There is a so-called sub-study included in this study. This sub-study aims at gaining a deeper understanding of the mechanisms by which AK001 may impact nasal polyps.

Study objective

Primary objective:
To evaluate the effect of each of 2 doses of AK001 separately in combination with an INS versus the INS alone on the reduction in size of nasal polyps as evaluated by the change from Baseline to Week 12 after the start of treatment in Total Polyp Score (TPS).

Secundary objectives:
1. To evaluate the effect of each of 2 doses of AK001 separately in combination with an INS versus the INS alone on changes from Baseline to Week 12 after the start of treatment in:
a) Size of polyps as evaluated by Lund-Mackay score at selected sites by computed tomography (CT) scan
b) Nasal airway patency as evaluated by peak nasal inspiratory flow (PNIF)
c) Ability to smell (University of Pennsylvania Smell Identification Test* [UPSIT])
d) Patient-reported symptoms of sinusitis (Sino nasal Outcome Test-22 [SNOT 22] and Visual Analogue Scales [VASs])
e) Quality of life (36-Item Short Form Health Survey [SF-36])
2. To evaluate the time to first response in TPS
3. To evaluate the change in TPS, UPSIT, and patient reported symptoms of sinusitis over time
4. To evaluate the safety and tolerability of each of 2 doses of AK001 separately in combination with an INS during 7 weeks of study drug in patients with moderate tosevere nasal polyps and whose symptoms are resistant to INSs

For the sub-study:
1. To evalaute baseline and after treatment levels of biomarkers related to the activity of mastcells and eosinophils in nasal secretions and blood.

Study design

This is a Phase 2, randomized, double-blind, placebo controlled study of the safety and tolerability of AK001 compared with placebo in patients with moderate to severe chronic nasal polyposis and whose symptoms are resistant to treatment with INSs. At least 50% of patients enrolled will have comorbid asthma.
The study will comprise an up to 4-week Screening period and a 4 week Run-in period followed by randomization and dosing with AK001 or placebo for 7 weeks followed by a 9 week observation (Post-treatment) period. There will be 9 scheduled study visits. The total duration of the study will be up to 24 weeks. After the Screening period, approximately 70 eligible patients will be enrolled and enter a Run-in period of 4 weeks to achieve a stable regimen with a common intranasal topical steroid (NASONEX [mometasone furoate monohydrate] 2 sprays in each nostril twice a day) and discontinue any other intranasal topical steroid. Patients will return to the clinic at the end of the Run-in period prior to dosing with study drug for pre dose evaluations. Patients who continue to meet the eligibility criteria for the study will be randomized, will continue to use NASONEX, and will also receive either 25 mg of AK001 (n=25), 250 mg of AK001 (n=25), or a corresponding placebo (n=20) on Days 0, 21, and 49. The randomization will be stratified based on presence or absence of asthma. Patients will be required to maintain their Baseline treatments for nasal polyposis unchanged throughout participation in this trial. A Data Monitoring Committee will be convened periodically to monitor the safety of patients over the course of the study.

Intervention

Intravenous infusion of 25 or 250 mg AK001 or placebo.

Study burden and risks

The intravenous administration of the study medication may lead to allergic reactions.

Contacts

Public
MediServ

De Stadspoort 32
Eindhoven 5611 GZ
NL
Scientific
MediServ

De Stadspoort 32
Eindhoven 5611 GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients are eligible for the study if all of the following criteria are met:
1. Written informed consent
2. Male and female patients aged *18 and *75 years at the time of Screening
3. SNOT-22 *30
4. TPS of *5 for both nostrils with presence on endoscopy of nasal polyps of grade *2 in each nostril according to the polyp grading scale and despite prior INS treatment for at least 8 weeks before Screening
5. History of at least 2 of the following symptoms for more than 4 weeks prior to Screening:
a) Anterior nasal discharge
b) Posterior nasal discharge
c) Nasal congestion, blockade, or obstruction
d) Decreased sense of smell
e) Facial pain or pressure
6. Received continuous topical nasal steroids and/or leukotriene receptor antagonists for at least 8 weeks prior to Screening
7. At randomization, received *80% of doses of NASONEX scheduled during the 4-week Run-in period
8. At randomization, TPS of *5 for both nostrils with presence on endoscopy of nasal polyps of

grade *2 in each nostril according to the polyp grading scale (see Inclusion Criterion #4) and despite prior INS treatment during the Run-in period
9. Female patients must be post-menopausal for *1 year with documented follicle-stimulating hormone (FSH) >30 IU/L, surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or, if of child-bearing potential, willing to use a highly effective method of contraception from Screening through the end of the study
10. Male patients with female partners of childbearing potential must agree to use a highly effective method of contraception from Screening until the end of the study. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
11. Negative Screening ova and parasite test
12. No clinically significant Screening 12-lead ECG, vital sign, hematology, chemistry, or urinalysis findings
13. Able to comply with all study procedures including recording scores of symptoms (i.e., anterior nasal discharge; posterior nasal discharge, nasal congestion, blockade, or obstruction; decreased sense of smell; facial pain or pressure) at clinic visits
Additional inclusion criteria sub-study:
1. Written informed consent to participate
2. Able to comply with all sub-study requirements (procedures and clinic visits)

Exclusion criteria

Patients are ineligible for the study if any of the following criteria are met:
1. Use of systemic corticosteroids within 6 weeks prior to Screening (or 5 half-lives, whichever is longer) or scheduled to receive systemic corticosteroids
2. Chronic use of antibiotic therapy within 3 months prior to Screening
3. Receipt of short-term antibiotic therapy within 14 days prior to Screening or use of antibiotics during the Screening period
4. Nasal surgery (including polypectomy) within 6 months prior to Screening
5. Significant mechanical nasal airway obstruction due to septal deviation based on Investigator assessment
6. Use of investigational drugs or participation in another clinical trial within 30 days prior to Screening or 5 half-lives, whichever is longer
7. Use of any medications that may interfere with the study, such as immunosuppressive drugs during the 2 weeks before Screening, or expected to require such medications through Day 112
8. Pregnancy or lactation in women
9. In patients with comorbid asthma, either of the following:
a) A FEV1 *60% at Screening
b) An asthma exacerbation requiring systemic (oral and/or parenteral) steroid treatment or hospitalization for >24 hours for treatment of asthma within 30 days prior to Screening
10. History of human immunodeficiency virus infection or other severe immunosuppressive disease
11. Current diagnosis or prior history of allergic fungal sinusitis, cystic fibrosis, ciliary

dyskinesia, Wegener*s Granulomatosis, or Churg-Strauss syndrome
12. Current diagnosis or prior history of any other condition likely to present with non-eosinophilic nasal polyps

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-09-2016
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	niet van toepassing

Ethics review

Approved WMO

Date:	26-04-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	07-07-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2016-000460-42-NL
CCMO	NL57341.018.16