A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial to Evaluate Efficacy and Safety of Lenabasum in Cystic Fibrosis

Published: 20-06-2018
Last updated: 11-04-2024

Primary efficacy objectives:To evaluate the efficacy of lenabasum 20 mg twice per day (BID) compared to placebo in the treatment of cystic fibrosis (CF) by assessing the rate of pulmonary exacerbations (PEx) using primary definition of PEx.Secondary…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital respiratory tract disorders
Study type	Interventional

Summary

ID

NL-OMON48813

Source
ToetsingOnline

Brief title
An efficacy and safety study of Lenabasum in Cystic Fibrosis

Condition

- Congenital respiratory tract disorders

Synonym
cystic fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Corbus Pharmaceuticals, Inc.

Source(s) of monetary or material Support: Corbus Pharmaceuticals;Inc.

Intervention

Keyword: Cystic Fibrosis, Efficacy, Safety, Selective Cannabinoid Receptor Type 2 Agonist

Outcome measures

Primary outcome

Rate of PEx using primary definition of pulmonary exacerbations (PEx) with lenabasum 20 mg BID, compared to placebo, during the treatment period

PEx definition for primary endpoint:

* Prescription of new oral, intravenous or inhaled antibiotics (regularly given prophylactic antibiotics do not count as new antibiotic unless the dose is increased, or given off schedule)

* At least 4 out of 12 Fuch*s criteria being met

Note: For a new exacerbation event, there needs to be at least 28-day gap from last use of antibiotics to the new antibiotics (regularly given prophylactic antibiotics do not count to determine the gap)

Secondary outcome

1. Efficacy of lenabasum 20 mg BID:

a. Event rate of PEx using secondary definition of PEx with lenabasum 20 mg BID compared to placebo

b. Time to first new PEx using primary definition of PEx with lenabasum 20 mg BID compared to placebo

c. Time to first PEx using secondary definition of PEx with lenabasum 20 mg BID compared to placebo

d. Change from baseline in CFQ-R respiratory symptom domain with lenabasum 20 mg BID compared to placebo

e. Change from baseline in FEV1 % predicted with lenabasum 20 mg BID compared to placebo

2. Efficacy of lenabasum 5 mg BID:

a. Rate of pulmonary exacerbations (PEx) using primary definition of PEx with lenabasum 5 mg BID compared to placebo, during the treatment period

b. Event rate of PEx using secondary definition of PEx with lenabasum 5 mg BID compared to placebo

c. Time to first new PEx using primary definition of PEx with lenabasum 5 mg BID compared to placebo

d. Time to first PEx using secondary definition of PEx with lenabasum 5 mg BID compared to placebo

e. Change from baseline in CFQ-R respiratory symptom domain with lenabasum 5 mg BID compared to placebo

f. Change from baseline in FEV1 % predicted with lenabasum 5 mg BID compared to placebo

3. PK endpoints:

a. Estimated trough plasma concentrations of lenabasum

b. Estimated maximum plasma concentrations (Cmax) of lenabasum

c. Metabolites of lenabasum

4. Safety endpoints

a. Treatment related Adverse Events (TEAEs)

b. Changes in vital signs, physical examination, blood and urine laboratory

safety tests and electrocardiograms

c. Treatment discontinuations with lenabasum compared to placebo

Secondary definition of PEx:

* Physician diagnosis of pulmonary exacerbation

* New antibiotics- oral, intravenous or inhaled, with same 28-day gap as above

from the last antibiotic use

Study description

Background summary

Cystic fibrosis is an autosomal recessive genetic disorder that affects multiple organs, including the lungs, pancreas, liver, and intestine. Cystic fibrosis is caused by one of many different disease-causing mutations in the gene for the cystic fibrosis transmembrane conductance regulator (CFTR), a cyclic AMP-dependent chloride channel (Kunzelmann et al, 2013). Mutations in CFTR on airway epithelial cells in CF lead to defective Cl- secretion and Na+ hyperabsorption by airway epithelia (Knowles et al, 1983). CFTR also are found on cells of the immune system, such as neutrophils (Painter et al, 2006), monocytes (Ettorre et al, 2014), and T cells (Shanshiashvili et al, 2012), where loss of CFTR function leads to abnormal immune cellular function. In CF patients, disease-causing mutations in CFTR lead to abnormally thick mucus (Burgel et al, 2007) and aberrant immune responses (Cantin et al, 2015, Ratner and Mueller, 2012).

The net result is a propensity in CF patients for recurrent infections and over-exuberant, yet ineffective leukocyte recruitment, phagocytosis, killing, and clearance of pathogens. The bioburden of bacteria in the lungs is high with the microbiome skewed toward pathogens such as Pseudomonas aeruginosa (P. aeruginosa). Chronic lung infiltration with neutrophils and release of neutrophil elastase and other enzymes contribute to bronchiectasis and

pulmonary fibrosis, which are a major cause of morbidity and mortality in CF.

Abnormalities in innate immune responses that lead to chronic inflammation contribute to the pathogenesis of CF (Hartl et al, 2012). These abnormalities include a decreased ratio of pro-resolving to pro-inflammatory lipid mediators (Karp et al, 2004, Ringholz et al, 2014a Ringholz et al, 2014b), increased production of proinflammatory chemokines, such as interleukin (IL)-8 (Kim et al, 2013, Wojewodka et al, 2014), abnormal cell surface expression of toll-like receptors (TLRs), such as TLR5 (Simonin-Le Jeune et al, 2013), and enhanced or impaired signaling through TLRs. The abnormalities of innate immunity extend to functional disturbances in neutrophils (Ng et al, 2014), ineffective bacterial uptake and subsequent killing by immune cells, reduced autophagy and cellular apoptosis in phagocytes (Mayer et al, 2013), and decreased clearance of apoptotic cells.
Among the abnormalities of innate immunity reported in CF is the inadequate production of *Specialized Pro-resolving lipid Mediators* (SPMs) which are molecules that initiate the physiologic process of resolution of inflammation. The relative overproduction of pro-inflammatory lipid mediators to SPMs in CF (Karp et al, 2004, Urbach et al, 2013, Ringholz et al, 2014a, Ringholz et al, 2014b) provides a mechanistic link to the failure of CF patients to resolve inflammation.

In CF, the ratio of SPMs to pro-inflammatory mediators is disproportionately low, tissue inflammation is excessive and persistent, pathogens are not effectively cleared, and tissue fibrosis leads to irreversible loss of structural damage to lungs. Of note, the ratio of a key SPM, lipoxin A4, to a key proinflammatory lipid mediator leukotriene B4 is low in bronchoalveolar lavage fluid of CF patients (Karp et al, 2004), even in the absence of infection (Ringholz et al, 2014a). Lipoxin A4 is produced by lipoxygenase interactions resulting from trans-cellular cooperation of neutrophils, eosinophils, alveolar macrophages, platelets or airway epithelial cells, each expressing different lipoxygenase enzymes, which act in sequence in lipoxin A4 biosynthesis (reviewed in Urbach et al, 2013). Normally, CFTR are expressed on both neutrophils and platelets, and neutrophil-platelet interactions during acute inflammation initiate lipoxin A4 production (Serhan and Sheppard, 1990). Platelets from patients with CF produce about 40% less lipoxin A4 than healthy subjects (Mattoscio et al, 2010). In addition, 15-lipoxygenase expression, which is required for lipoxin A4 production, is reduced in CF (Ringholz et al, 2014a). In animal models of CF, mice deficient in CFTR have reduced production of lipoxin A4 by neutrophils and platelets (Wu et al, 2014). Importantly, in turn, lipoxin A4 increases CFTR protein expression (Yang et al, 2012).

Lenabasum is a synthetic molecule that activates resolution of inflammation. It is a preferential cannabinoid receptor type 2 (CB2) full agonist that has 12-fold greater affinity for CB2 than cannabinoid receptor type 1 (CB1) (Tepper et al, 2014). Lenabasum shows little evidence of psychotropic activity at likely therapeutic doses, because of limited ability to cross the blood-brain

barrier and reduced affinity for CB1.
There are two major CB receptor subtypes: CB1, mainly expressed in the central and peripheral nervous system; and CB2, mainly distributed throughout immune and hematopoietic cells, epithelial cells, fibroblasts, osteoblasts, skin keratinocytes, and the peripheral nervous system (Rom and Persidsky, 2013). CB2 is preferentially expressed on activated immune cells.

Lenabasum induces *class switch* of arachidonic acid metabolism from proinflammatory lipid mediators to SPMs through effects on 15-lipoxygenase (Zurier et al, 2009) and possibly other lipid metabolizing enzymes. Agonists of CB2 are known to increase production of anti-inflammatory eicosanoids, such as prostaglandin (PG) J2 and cytokines, such as IL-10 (Shanshiashvili et al, 2012). Further, CB2 agonists including lenabasum can induce apoptosis of T cells (Bidinger et al, 2003, Singh et al, 2012), and fibroblasts (Garcia-Gonzalez et al, 2009). Of direct relevance to treatment of CF, endocannabinoids and synthetic CB2 agonists blunt inflammation, innate immune responses and deposition of extracellular matrix, by:
* Inhibiting expression of TLR and nucleotide-binding oligomerization domain (NOD)-like receptors and TLR signal transduction (Downer et al, 2011, Duncan et al, 2013)
* Reducing production of early mediators of inflammation, including chemotactic factors, such as IL-8 (Selvi et al, 2008) and proinflammatory lipids
* Inhibiting tissue infiltration with leukocytes, by inhibiting leukocyte rolling and tissue infiltration (Mukhopadhyay et al, 2010), chemotaxis and differentiation of dendritic cells (Adhikary et al, 2012)
* Reducing production of proinflammatory cytokines by these infiltrating cells, including type 1 interferons, IL-1*, IL-6, tumor necrosis factor * (TNF*) and IL-17 (Zurier et al, 2003, Parker et al, 2008, Selvi et al, 2008, Kong et al, 2014)
* Inhibiting accumulation of myofibroblasts, production of transforming growth factor-* (TGF*), connective tissue growth factor, and extracellular matrix components (Akhmetshina et al, 2009, Gonzalez et al, 2012, Börgeson et al, 2011, data on file)
Class switching of lipid mediators (Levy et al, 2001) to favor production of lipoxin A4 and other SPMs would be expected to have therapeutic benefit in CF, through effects on multiple pathologic pathways in CF. As examples, lipoxin A4:
* Enhances CFTR protein expression, at least in rat lungs (Yang et al, 2012)
* Decreases mucus thickness through effects on ion transport (Al-Alwani et al, 2014, Verrière et al, 2012)
* Increases airway epithelium integrity (Buchanan et al, 2013)
* Attenuates pulmonary fibrosis (Martins et al, 2009, Krönke et al, 2012).
Lipoxin A4 inhibits fibroblast proliferation (Wu et al, 2006) and TGF* receptor type 1 expression and responses to TGF* (Brennan et al, 2013, Börgeson et al, 2011). Of note, high producer TGF*1 genotypes are associated with severe lung disease in CF (Arkwright et al, 2000), TGF-* signaling and fibrosis are markedly increased in CF (Harris et al, 2013) and TGF* may interfere with therapies directed at correcting the processing defect in CFTR in CF patients

(Snodgrass et al, 2013).

Therapeutic approaches to reduce inflammation in patients with CF have shown clinical benefit, such as alternate-day corticosteroids and high dose ibuprofen (Konstan et al, 2007), but adverse effects and other considerations have limited their use. Alternative agents to reduce lung inflammation and resulting fibrosis are needed. The development of new therapies that will do this is a strategic priority for the Cystic Fibrosis Foundation.

Lenabasum is being investigated as a new therapy for CF because of its potential to resolve inflammation and stop pro-fibrotic processes in CF. Lenabasum triggers the physiologic process of resolution of inflammation. It reduces levels of pro-inflammatory mediators and increases levels of SPMs including lipoxins and resolvins in involved tissues. Lenabasum reduces polymorphonuclear leukocyte infiltrates and improves bacterial clearance in the lungs in a mouse model of infection-induced inflammation in CF. Similarly, lenabasum reduces polymorphonuclear infiltration and pro-inflammatory mediators while hastening bacterial clearance in a human model of infection-induced innate immune response in the skin.

Study objective

Primary efficacy objectives:
To evaluate the efficacy of lenabasum 20 mg twice per day (BID) compared to placebo in the treatment of cystic fibrosis (CF) by assessing the rate of pulmonary exacerbations (PEx) using primary definition of PEx.

Secondary efficacy objectives:
1. To evaluate the efficacy of lenabasum 20 mg BID compared to placebo in the treatment of CF by assessing other efficacy endpoints
2. To evaluate the efficacy of lenabasum 5 mg BID compared to placebo in the treatment of CF

Pharmacokinetic (PK) objectives:
1. To evaluate steady state plasma concentrations of lenabasum 20 mg BID and lenabasum 5 mg BID at the estimated time of trough concentration after a dose of lenabasum
2. To evaluate plasma concentrations of lenabasum 20 mg and 5 mg at the estimated time of peak concentration after the first dose
3. To evaluate metabolites of lenabasum
4. To develop population pharmacokinetic models of lenabasum in Cystic Fibrosis subjects

Safety objectives:
1. To evaluate safety of lenabasum 20 mg BID and lenabasum 5 mg BID treatment and placebo treatment
2. To evaluate tolerability of lenabasum 20 mg BID and lenabasum 5 mg BID

treatment

Study design

This is a double-blind multi-center study to evaluate efficacy and safety of lenabasum in subjects with Cystic Fibrosis (CF). About 100 investigator sites in North America, Canada, Europe, Israel and Australia. Approximately 415 subjects will be eligable for enrollment in this study. Patients will attend a screening visit where the following assessments will take place in order to determine eligibility: Physician assessment of pulmonary exacerbations (PEx)- which is called the Antibiotic Use for Respiratory Signs and Symptoms Questionnaire (AUR-Q),concomitant medication check, contraceptive check, spirometry, CRISS and CFQ-R questionnaires, adverse events, vital signs (consisting of systolic and diastolic blood pressure (BP), pulse rate (P), respiratory rate (R), body temperature (T), weight, height, and O2 saturation), common CF pathogens in sputum, ECG, biomarkers and laboratory safety tests.

If the patient is eligible following these assessments they will be randomized centrally to one of three treatment groups* 5 mg twice a day (BID), 20 mg BID or placebo BID, in a 2:1:2 ratio. Subjects who receive at least one dose of study drug will be considered enrolled in the study.

Active dosing with study drug is 28 weeks. There will be 8 scheduled study visits during active dosing with study drug, labeled Visits 1-8. Visits occur at Visit 1 and at the completion of Weeks 4, 8, 12, 16, 20, 24, and 28 ± 1 week). Subjects who complete Visit 8 on study drug will have a Safety Follow-up Visit labeled Visit 9 at the completion of Week 32. All subjects who develop acute signs and symptoms of worsening lung disease will be asked to return to the site for evaluation at a Possible PEx Visit. Unscheduled Visits may be necessary to assess the subject for safety purposes unrelated to new respiratory symptoms or a PEx.

The following items will be assessed at all study visits: Physician assessment of PEx (AUR Questionnaire),concomitant medication check, contraceptive check, Spirometry, CRISS questionnaires, BMI, Adverse events, Vital signs (consisting of systolic and diastolic blood pressure (BP), pulse rate (P), respiratory rate (R), body temperature (T), weight, height, and O2 saturation) and Laboratory safety tests. In addition, CFQ-R questionnaire and

Common CF pathogens in sputum will be completed at visits 1,5, 8 and possible PEx visits. ECGs will be completed
at visits 1,5 and 8 only. Biomarkers for blood and sputum will take place at Visits 1,2,5, 8 and possible PEx visits.
Plasma sampling for Lenabasum and metabolites will be completed at visit 1 before and 3±0.5 hours after
administration of first drug dose, at visit 2, 5 and 8 the sample will be taken 8 - 16 hours after the last intake of study
drug.

This trial includes analyses of time to and event rate of PEx. In this study, a PEx is defined as a clinical event of new or
worsening pulmonary or systemic symptoms beyond normal day-to-day variation that causes the physician to treat
with systemic antibiotics. There is no interim analysis planned.

Intervention

Subjects will be allocated to receive either 5 mg IMP twice a day or 20 mg IMP twice a day - or matching placebo. Both are referred to as Study Drug/IMP. Each subject will be receive Study Drug for 28 weeks.

Study burden and risks

Lenabasum is an investigational medicinal product and has not been approved for any indication, therefore, it is not guaranteed that enrolled subjects will experience a clinical benefit from participation in this clinical study.
However, the potential for clinical benefit is supported by data obtained from previously completed Phase 2 clinical trials in Cystic Fibrosis and diffuse cutaneous SSc. In addition, the data from this study may have an indirect benefit in that it will be used to further understand and characterize the safety and potential clinical benefit of lenabasum and may therefore help other Cystic Fibrosis patients by contributing to medical research. The results of this study are expected to provide further insight into the efficacy, safety, and tolerability of lenabasum in patients with Cystic Fibrosis.

Prior to this study Lenabasum has been safely administered to ~250 subjects (both healthy and in patients with serious inflammatory disease), up to a total daily dose up to 240 mg, and at dose of 40 mg/day for a period of more than 12 months.
Corbus were notified of 2 SUSARs originating from the US sites participating in the JBT101-CF-002 study. The events reported were acute pulmonary exacerbation (US-CORBUS-0037) and pulmonary exacerbation of cystic fibrosis (US-CORBUS-0064). As of 05 Mar 2019, 480 subjects have been exposed to blinded Lenabasum or placebo, including 223 subjects enrolled in CF studies. Of those, 138 patients are enrolled in the CF-002 study. As of 02 Apr 2019, 14

and 10 (blinded) subjects experienced serious PEx in the CF-001 and CF-002 studies, respectively. In study CF-001, 14 subjects reported serious PEx; 8 of whom received a dose of Lenabasum. The rate of serious PEx is currently approximately 10.8% across both Corbus-sponsored CF studies, with study JBT101-CF-002 remaining blinded, which is within the anticipated rate of occurrence in the enrolled population. There were no SARs reported in other Lenabasum trials to date and no significant difference in the rate of infections between Lenabasum and placebo was identified in unblinded reported studies.

Overall, lenabasum has been found to be well-tolerated in clinical studies conducted to date with only mild or moderate adverse reactions observed. The most common adverse reactions consistent with the pharmacological action of lenabasum during placebo-controlled dosing has been dizziness in SSc and dry mouth in CF study. Together, results from the preclinical safety, toxicology and pharmacokinetic studies, efficacy studies in animal models of disease, studies with human biomaterials, as well as safety and preliminary efficacy in humans support a favorable benefit-risk profile of lenabasum. These data justify its continuing investigation in clinical trials in rare and serious autoimmune/inflammatory disorders, with significant unmet medical need, such as Cystic Fibrosis.

The potential burden and risk of participation in this study are not expected to be different from other comparable clinical research studies. There are 8 planned weekly visits, plus screening and a possible Safety Follow-up visit, labelled Visit 9, and every effort will b made to be respectful of the subjects' time. The design of this study was developed on input from the US Food and Drug Administration, Cystic Fibrosis Foundation, European Cystic Fibrosis society and US and EU Co-Principal Investigators.

Blood and urine samples will be taken at all 9 visits and patients will be asked to provide sputum samples, preferably spontaneously but induced where not possible. Blood sampling may cause minor discomfort and occasionally may cause bruising or inflammation of the place
where the blood was drawn. Only trained clinical staff and the medical staff will perform the procedure. At each visit patients will be required to complete 3 questionnaires. To reduce the burden associated with completing these questionnaires, a table will be utilised to collect subject responses electronically. An electro cardiogram will be performed 3 times during the study. Risk associated with this test is minimal, where localised skin irritation from the gel pads is rarely seen. Subjects will be required to perform spirometry at each study visit. Spirometry may result in coughing, shortness of breath, dizziness and headache; which are temporary. Spirometry is performed during normal clinical care to assess disease progression in patient lungs.

The most common adverse reaction observed in reported lenabasum studies is

dizziness, often described as lightheadedness, that is usually mild and transient. An individual subject should not receive any further study product if any serious AE related to lenabasum occurs. To potentially reduce drop-out rates from AEs or tolerability issues during the study, the treating physician may choose to reduce the dose of study product by 1 capsule per day. This decision should be discussed with the Medical Monitor for consensus prior to instituting any reduction. The impact of any reduction in dose will be assessed in sensitivity analyses of efficacy outcomes. AE monitoring will be carried out at each visit. Additionally, subjects will be instructed to call study personnel to report any abnormalities during the intervals between study visits and to come to the site if medical evaluation is needed and the urgency of the situation permits. An unscheduled visit will be made, if necessary, for medical issues that arise between study visits.

Studies of human reproduction have not been performed with lenabasum. It is not known whether lenabasum can cause foetal harm when administered to pregnant women or whether it can negatively affect reproduction. Female and male participants will be asked to use adequate contraception.If a female participant becomes pregnant during the study, she will be instructed to inform the trial doctor immediately. All participants who become pregnant during the study will discontinue study drug and be removed from the study. The pregnancy will be reported and the outcome reported, once known.

This study will include adolescent subjects with ages 12 to 17 years and body weight * 40 kg. According to the Cystic Fibrosis Foundation 2015 Patient Registry report, CF patients are at an increased risk of pulmonary exacerbations increasing with age from adolescence to early adulthood, therefore adolescents represent an important at-risk population for the planned indication investigated in this study. The investigated doses of lenabasum 20 mg BID and lenabasum 5 mg BID that are proposed for the Phase 2 CF study, predict systemic exposure (i.e., AUC and Cmax) of lenabasum in adolescents age 12-17 years to be similar to that in adults (refer to section 5.4.6 in IB). In addition, the safety of treatment of adolescents with lenabasum at 20 mg BID is supported by analyses of nonclinical studies of lenabasum pharmacology, toxicology and metabolism (refer to section 4.2 in IB). All adolescent subjects will be required to sign on both Assent Form and Parental ICF before they get enrolled into the study.

Lenabasum is a Selective Cannabinoid Receptor Type 2 Agonist. Lenabasum has shown low potential for abuse in
preclinical and evidence of psychotropic effects of the study product in subjects is being tested in other ongoing trials
using the Addiction Research Center Inventory-Marijuana Test.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Documentation of a CF diagnosis as evidenced by 1 or more clinical features consistent with the CF phenotype and 1 or more of the following criteria:
a. Sweat chloride * 60 mEq/L by quantitative pilocarpine iontophoresis test
b. Two known disease-causing mutations in the CFTR gene.
2. Twelve years of age or older at the time Informed Consent/Assent is signed.
3. Weight * 40 kg.
4. FEV1 * 40% predicted and < 100 % predicted within the last 12 months.
5. Physician-initiated treatment with an IV antibiotic 2 or 3 times in the last 12 months for a new PEx.
6. As an alternative to inclusion criterion 5, physician-initiated treatment

with an IV antibiotic 1 time in the last 12 months plus physician-initiated treatment with oral antibiotic(s) 1 or more times in the past 12 months for a new PEx.
7. Completion of the last course of antibiotics prescribed for any PEx * 28 days before Visit 1.
8. Able to perform pulmonary function tests. Optional use of a bronchodilator before testing is allowed to facilitate testing if the bronchodilator is used consistently starting with Visit 1.
9. Willing to provide repeat sputum specimens. If a subject is unable to reliably spontaneously expectorate sputum, induced sputum collection is acceptable. Optional collection of induced sputum specimens is allowed if induced sputum specimens are consistently collected starting with Visit 1. Adolescents should try to produce sputum spontaneously and can opt out of sputum induction.
10. Willing not to use any cannabinoids or any illegal substance of abuse from screening through Visit 9.
11. Women of childbearing potential must not be pregnant or breastfeeding at Visit 1 and must be using at least one highly effective or an acceptable method of contraception for at least 28 days before Visit 1 and be willing to continue to use at least one highly effective or an acceptable method of contraception throughout the study and for at least 28 days after discontinuation of study drug .
12. Male participants must be willing to follow contraceptive requirements and should not get anyone pregnant while thy are taking the study product or within 28 days after taking the last dose of the study product, during which time period they or their partner must be willing to use at least one highly effective or an acceptable method of contraception.
13. Able to adhere to the study visit schedule and other protocol requirements.

Exclusion criteria

1. Severe or unstable CF at screening or Visit 1, such as:
a. Change in dose, or initiation of any new chronic therapy for CF lung disease within 28 days before Visit 1
b. Treatment with any systemic corticosteroids > 10 mg per day prednisone or equivalent within 14 days before Visit;
c. Actively listed on an organ transplant list or have had an organ transplant other than corneal transplant.
2. Significant diseases or conditions other than CF that may influence response to the study drug or safety, such as:
a. Active hepatitis B or C infection
b. Human immunodeficiency virus infection
c. A history of cancer except basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy * one year before

Visit 1.
3. Subjects with a history of any seizure within the last 2 years
4. Pregnant, trying to become pregnant or lactating female.
5. Current evidence of alcohol abuse (defined as 4 or more drinks per day on at least 4 days of the week) or history of abuse of illegal and/or legally prescribed drugs such as barbiturates, benzodiazepines, amphetamines, cocaine, or opioids during the 1 year before screening.
6. Any investigational agent within 30 days or five therapeutic half-lives of that agent whichever is longer, before Visit 1
7. Any of the following values for laboratory tests at screening:
a. A positive pregnancy test
b. Hemoglobin < 10 g/dL in males and < 9 g/dL in females.
c. Neutrophils < 1.0 x 1000,000,000/L
d. Platelets < 75 x 1000,000,000/L
e. Creatinine clearance < 50 ml/min according to Modification of Diet in Renal Disease (MDRD) Study equation in adults and Schwartz eGRF formula in adolescent population.
f. Serum transaminases > 2.5 x upper normal limit
8. Any other condition or concurrent medical therapy at screening or Visit 1 that causes the investigator to determine it is not safe for the subject to participate or that may influence response to study drug or interfere with study assessments.

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):	14-08-2019

Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lenabasum
Generic name:	Lenabasum

Ethics review

Approved WMO Date:	20-06-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-05-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	23-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2017-003723-29-NL
ClinicalTrials.gov	NCT03451045
CCMO	NL65181.091.18