Randomized placebo-controlled multicenter exploratory Phase IIA study to assess the safety and efficacy of PEG-liposomal prednisolone sodium phosphate (Nanocort) in subjects with active ulcerative colitis.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON40072

Source
ToetsingOnline

Brief title
ENC-0303-CL-203

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflammatory bowel disease (IBD), Ulcerative Colitis (UC)

Research involving

Human

Sponsors and support

Primary sponsor: Enceladus Pharmaceuticals
Source(s) of monetary or material Support: Sponsoring via Enceladus Pharmaceuticals;Sint Annastraat 38A;1411PH Naarden;Nederland

Intervention

Keyword: Nanocort, PEG-liposomal prednisolone, Ulcerative Colitis (UC)

Outcome measures

Primary outcome

All (serious) adverse events will be classified according "MedDRA"

Primary Endpoints (safety):

Frequency of Serious adverse events in Nanocort versus placebo group

Frequency of Adverse events in Nanocort versus placebo group

Changes in clinical status, vital signs and laboratory parameters over the duration of the study in Nanocort versus placebo group.

The number of adverse events, the number and percentage of subjects who reported at least one adverse event will be provided by treatment group and by system organ class and preferred term, the severity, causality of the event.
The number of adverse events, the number and percentage of subjects who reported at least one serious adverse event (reported during all the study period) will be provided by treatment group and by system organ class and preferred term.

Descriptive statistics will be presented at relevant visits by treatment group

for physical examination and clinical status, vital signs and laboratory assessments.

The number of subjects with laboratory parameter values out of the reference ranges will be computed at each visit. Shift tables will count the number of subjects with normal and abnormal values at the last visit of the treatment phase with

The number of adverse events, the number and percentage of subjects who reported at least one adverse event will be provided by treatment group and by system organ class and preferred term, the severity, causality of the event.
Serious adverse events (reported during all the study period).

Secondary outcome

Secondary Endpoints (efficacy/PK):

Percentage of subjects achieving clinical remission at Day 29 as measured by Mayo score in Nanocort versus placebo group.
Percentage of subjects achieving clinical remission at Day 15, 29, 57 and 85 as measured by partial Mayo score in Nanocort versus placebo group. Percentage of subjects achieving clinical response at Day 15, 29, 57 and 85 as measured by partial Mayo score in Nanocort versus placebo group.
Percentage of subjects maintaining a clinical response in Nanocort versus placebo group, in subjects having previously achieved a clinical response after baseline evaluations.

Scoring the histopathological asessments on biopsies by microscopic evaluation (acute inflammation score and grading scale of inflammation) in Nanocort versus placebo group.

Free prednisolone and liposomal prednisolone phosphate levels in the plasma at Day 1, 15, 29 and 57 in Nanocort versus placebo group.

Definitions:

Clinical remission is defined as a Mayo score <= 2 with no individual sub-score exceeding 1 point and rectal bleeding score of 0.

Clinical response is defined as a reduction from base-line Mayo score of 30% or >= 3 points, with an accompanying decrease in rectal bleeding sub-score of >= 1 point or absolute rectal bleeding score of <= 1 point.

Study description

Background summary

Nanocort is a novel pharmaceutical composed of prednisolone sodium phosphate enclosed in carefully designed small lipid vesicles, which after IV infusion selectively accumulate in inflamed tissues. The corticosteroid is largely confined to the liposome in the blood stream after injection, and selectively accumulates at sites of inflammation forming local depots. This effect is possibly due to locally increased permeability of blood vessel walls at inflamed sites. High local concentrations of corticosteroids may have a more pronounced effect on the reduction of inflammatory cells and mediators. As a result, Nanocort might be able to significantly reduce frequency of administration and use of the steroid compared to the treatment with oral steroids and so has a safety advantage.

Study objective

The primary objective is to evaluate the safety of PEG-liposomal prednisolone sodium phosphate (Nanocort)

The secondary objectives of this study are:
To explore the efficacy of PEG-liposomal prednisolone sodium phosphate (Nanocort)
To evaluate the pharmacokinetics of free prednisolone and prednisolone phosphate in the plasma.

Study design

The study is an exploratory phase IIA, randomized, placebo-controlled multicenter international study.
A total of 20 subjects with active UC will be randomized.

Intervention

The 20 randomized subjects with active UC will be distributed randomly into two groups with a 3:1 ratio (15 subjects to receive Nanocort). In this study, each group will receive two IV infusions either saline (placebo) or PEG-liposomal prednisolone sodium phosphate (Nanocort) in saline.
Treatment consists in 2 IV infusions administered two weeks apart on day 1 and on day 15.

Fifteen subjects will receive PEG-liposomal prednisolone sodium phosphate (Nanocort) in saline at Day 1 and Day 15 as an IV infusion of 150 mg Nanocort in 250 mL saline.
Five subjects will receive a 250 mL infusion with saline (placebo) on Day 1 and Day 15.
Follow-up clinical visits will occur at Day 29, 57 and 85 after treatment was initiated.

Study burden and risks

The total expected duration of subject participation will be approximately 14 weeks; 2 weeks of screening, 2 weeks of treatment visits, and post-treatment follow-up visits 2, 6 and 10 weeks after the completion of study treatment (a total of 6 visits).

During the visits, the investigator will perform, besides the normal clinical procedures, an additional full physical examination.
Dring each visit urine and blood will be collected.
Sigmoidoscopy with imaging and collection of 2 to 4 biopsies will be performed twice (during screening visit and day 29)

At three time points a 24h urine collection will be requested to determine the influence of Nanocort on the cortisol levels
On visit 1, serology for HIV, HBV and HCV will be checked.
On visits 2,3,4 and 5 additional blood will be taken to perform the

pharmacokinetics analysis. (PK)

Contacts

Public
Enceladus Pharmaceuticals

Sint Annastraat 38A
Naarden 1411PH
NL
Scientific
Enceladus Pharmaceuticals

Sint Annastraat 38A
Naarden 1411PH
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1.Male or non pregnant, non-lactating female >= 18 to 75 years of age.
2.Documented history of UC (at least 6 months) as assessed by endoscopy and confirmed by histological measurements with a minimal disease extent of 15 cm from the anal verge and a minimal period of moderately active disease of 14 days.
3.Negative stool culture for enteric pathogens, including Clostridium difficile, ova and parasites.
4.Mayo score >= 5 with endoscopic sub-score of >= 2 and rectal bleeding sub-score >=1.
5.Medication: 6-MP/azathioprine, MTX receiving for at least 12 weeks and stable dose for > 4 weeks or discontinued for > 4 weeks; rectal medications stopped for > 4 weeks, 5-ASA stable

or stopped for > 2 weeks. If receiving cyclosporine or biologicals (e.g. TNFα blocker), these medications should be continued at the same dose for at least two cycles after Day 1. A cycle commonly takes 8 weeks, but may be shorter in the individual subject, when loss of response has been encountered previously and the dosing interval has been adjusted.
6.In good physical and mental health (other than the disease under study) as determined by medical history and physical examination.
7.The results of the following laboratory tests performed at the local laboratory at screening must be as below:
a.Hemoglobin >= 8.5 g/dL (International System of Units [SI]: >= 85 g/L)
b.White blood cells (WBC) >= 3.0 x 10E3 cells/mm3 (SI: >= 3.0 x109 cells/L)
c.Neutrophils >= 1.5 x 10E3 cells/mm3 (SI: >= 1.5 x109 cells/L)
d.Platelets >= 100 x 10E3 cells/mm3 (SI: >= 100 x109 cells/L)
e.Serum ALT <= 1.5 x upper limit of normal (ULN)
f.Total bilirubin level >= 1.25 x ULN
g.Creatinine clearance >80 mL/min using the Cockcroft formula
8.Female subjects must have a negative blood pregnancy test, unless they are surgically sterile, had a hysterectomy or have been post-menopausal for at least 1 year (at least 12 consecutive months without menses).
9.Women of childbearing potential must use a medically acceptable means of birth control and agree to continue its use during the study and for at least 12 weeks after the last dose of study drug. Medically acceptable forms of birth control include oral contraceptives, injectable or implantable methods, intrauterine devices, tubal ligation (if performed more than 1 year before screening), or double-barrier contraception. Sexually active men must agree to use a medically acceptable form of contraception during the study and continue for at least 12 weeks after the last dose of study drug.
10.Able and willing to give voluntary written informed consent and agree to schedule of assessments.

Exclusion criteria

1.Treatment with local or oral corticosteroids within 4 weeks of screening or with intra articular or intramuscular corticosteroids within 8 weeks before screening. If non-systemic steroids are being used for other chronic inflammatory conditions, subjects may be included at the discretion of the investigator after discussion with the medical monitor.
2. Severe colitis, defined as a bloody stool frequency of more than six per day with any one of tachycardia (pulse > 90 beats/min), temperature (> 37.8 degrees C), anaemia (haemoglobin < 10.5 g/dL or 6,5 mmol/L) or raised erythrocyte sedimentation rate (> 30 mm/h),
3.Intolerance of or unresponsiveness to corticosteroids, especially a history of steroid psychosis.
4.A history of significant psychological, neurologic, renal, gastrointestinal (other than ulcerative colitis), or metabolic disease. (diabetes mellitus)
5.A history of clinically severe or unstable medical condition involving cardiac, pulmonary, liver or endocrine disorders.
6.Any concurrent illness, disability or clinical abnormality (including laboratory tests) that may affect the interpretation of clinical safety or efficacy data or prevent the subject from

safely completing the assessments required by the protocol as determined by the investigator.
7.The subject has a Stoma, proctocolectomy or total colectomy or imminent need for surgery.
8.Concurrent bowel and/or intestine malignancy or a history of cancer (other than basal cell carcinoma or cervical carcinoma successfully treated more than 5 years prior to screening be allowed);
9.Subjects with other bleeding, infectious, ischemic, or immunological diseases with or without gastrointestinal involvement.
10.Be currently pregnant or breastfeeding or not willing to maintain birth control methods for at least 12 weeks after last study medication administration.
11.Medical, psychiatric, cognitive, or other conditions that, according to investigator*s medical judgment, compromise the patient's ability to understand the patient information, to give informed consent, to comply with requirements of the study the study protocol (that is likely to affect the patient*s return for visits on schedule), or ability to complete the study.
12.Participation in another experimental therapy study within 90 days prior to screening for this study or current enrollment in any other study with investigational drugs or device.
13.Positive serology for human immunodeficiency virus (HIV) 1 or 2 or hepatitis B or C, or any history of HIV or hepatitis from any cause with the exception of hepatitis A.

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):	08-10-2012
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nanocort
Generic name:	PEG-liposomal prednisolone sodium phosphate

Ethics review

Approved WMO Date:	20-10-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-12-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-05-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-06-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-04-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2010-020448-37-NL
CCMO	NL33742.041.10