Phase 1b, Multicenter, Randomized, Blinded, Placebo-controlled Study to Evaluate the Efficacy of Guselkumab in Subjects with Familial Adenomatous Polyposis

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To explore the effect of treatment with guselkumab in subjects with Familial Adenomatous Polyposis (FAP) on rectal/pouch polyp burden (the sum of the polyp diameters)

Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55226

Source
ToetsingOnline

Brief title
CNTO1959COR1001

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Familial Adenomatous Polyposis, FAP

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilag BV

Intervention

Keyword: Familial Adenomatous Polyposis, FAP, Guselkumab

Outcome measures

Primary outcome

Percentage change from baseline in rectal/pouch polyp burden at Week 24. Note

that there will be a placebo arm available for comparison.

Secondary outcome

• Percentage change in number of colorectal polyps

• Percentage change in number of J-pouch polyps

• Percentage change in J-pouch polyp burden

• Percentage change in number of duodenal polyps

• Percentage change in duodenal polyp burden

• Change in InSiGHT stage

• Change in Spigelman stage

• Trough concentration of guselkumab.

• The incidence and titers of antibodies to guselkumab

- Safety profile of guselkumab (safety parameters include but are not limited

to the frequency and severity of adverse events [AEs], vital signs, clinical

laboratory values).

- Changes in levels of IL-23 effector proteins relative to baseline levels in

biopsy tissue

Study description

Background summary

TREMFYA* (guselkumab) is a fully human immunoglobulin G1 lambda monoclonal antibody that binds to the p19 subunit of human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to IL-23 blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor (IL-23R), inhibiting IL-23-specific intracellular signaling and subsequent cell activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.
Guselkumab is currently approved in the United States, European Union, and other countries worldwide for the treatment of moderate to severe plaque psoriasis. In addition, guselkumab is being evaluated in several other immune-mediated diseases including generalized pustular psoriasis, erythrodermic psoriasis, palmoplantar pustulosis, hidradenitis suppurativa, psoriatic arthritis (PsA), and Crohn*s disease.

Familial adenomatous polyposis (FAP) is the most common polyposis syndrome. It is an autosomal dominant inherited disorder characterized by the early onset of hundreds to thousands of adenomatous polyps throughout the colon. If left untreated, nearly all individuals with this syndrome develop colorectal cancer (CRC) by the third decade of life. Prophylactic colectomy is the standard of care, but individuals remain at risk for malignant transformation of duodenal and rectal polyps for those who have undergone rectal-sparing surgeries. Individuals who undergo prophylactic colectomy generally retain rectal tissue in an attempt to preserve anal function. This is achieved through either an ileo-rectal anastomosis (IRA), which leaves about 10 cm of rectum, or an ileal pouch-anal anastomosis (IPAA), which only leaves about 2 to 4 cm of rectum. Multiple studies with both nonselective and selective cyclooxygenase inhibitors (such as sulindac or celecoxib) have shown that anti-inflammatory agents may prevent the formation and inhibit the growth of colorectal adenomatous polyps. However, toxicities associated with these agents have prevented their further development. Therefore, there is a high unmet need for novel treatment options to reduce polyp burden, delay or eliminate the need for colectomy and recurrent rectal surgery, and intercept the development of adenocarcinomas in individuals with FAP.

Polyps from individuals with FAP display inflammatory features associated with the activation of the IL-23/IL-17/JAK/STAT3 pathway.6 This inflammation is thought to contribute to further mutagenesis, culminating in tumor development. Specifically, IL-23 is linked to tumor growth and progression in CRC,5 and adenomas with high-grade dysplasia showed elevated levels of IL-17A and pSTAT3.3 Tumors from the Apcmin/+ mouse model of CRC showed elevated levels of IL-23 and IL-17A. Apc mutant mice deficient in IL-23 developed fewer tumors and less

inflammation.
Guselkumab, a human mAb directed against the p19 subunit of IL-23, specifically targets IL-23 and inhibits its interaction with the IL-23 receptor. A rapidly growing body of literature suggests that the IL-23/IL-17 pathway contributes to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases including psoriasis, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, and psoriatic arthritis. Pre-clinical models suggest that inhibition of IL-23 signaling will result in less inflammation and reduce tumor development.

Study objective

To explore the effect of treatment with guselkumab in subjects with Familial Adenomatous Polyposis (FAP) on rectal/pouch polyp burden (the sum of the polyp diameters)

Study design

OVERALL DESIGN
This is a Phase 1b, randomized, blinded, placebo-controlled, multicenter, proof-of-concept study to evaluate the preliminary clinical activity of guselkumab in subjects with FAP. The study is designed to determine if guselkumab has clinical activity in the colorectum and duodenum, by reducing the number of polyps over a period of 24 weeks. Once a subject is determined to be eligible for the study, the subject will be randomized to one of the 3 treatment arms.

All subjects will be randomized to 1 of 3 treatment groups in a 1:1:1 ratio as described below.
• Group 1: Guselkumab 100 mg subcutaneous (SC); 6 doses, administered every 4 weeks (Q4W)
• Group 2: Guselkumab 300 mg SC; 6 doses, administered Q4W
• Group 3: Placebo SC; 6 doses, administered Q4W
Subjects who respond to guselkumab at Week 24 will have the option to continue treatment through Week 48. All subjects will be monitored for 12 weeks following their last dose.

Intervention

• Group 1: Guselkumab 100 mg subcutaneous (SC); 6 doses, administered every 4 weeks (Q4W)
• Group 2: Guselkumab 300 mg SC; 6 doses, administered Q4W
• Group 3: Placebo SC; 6 doses, administered Q4W

Study burden and risks

This is the first study with guselkumab in subjects with FAP. Guselkumab selectively blocks IL-23, a cytokine that plays a key role in various inflammatory conditions. As this is a proof-of-concept study, there is no established benefit for the proposed indication, and the current safety profile of guselkumab shows that guselkumab has been well-tolerated. Thus, benefit risk remains acceptable for the proposed study in patients with FAP. Detailed information about the known and expected benefits and risks of guselkumab are provided in the guselkumab IB.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:
1. Males and females >=18 years of age.

2. Diagnosis of phenotypic FAP with disease involvement of the colorectum with either:
a. Genetic diagnosis: APC germline mutation (with or without family history) or obligate
carrier.
b. Clinical diagnosis: FAP phenotype with >100 adenomas in large intestine and subject has a family history of FAP.
c. Clinical diagnosis: FAP phenotype who are status post colectomy for polyposis, subject has a family history of FAP, and 2 FAP experts agree to the diagnosis.
d. Attenuated FAP diagnosis: APC germline mutation required.
3. Criterion modified per Amendment 3.
3.1. Post-colectomy or subtotal colectomy with ileocolonic anastomosis, IRA, or IPAA.
4. Polyps with a sum of diameters >=10 mm in the rectum or pouch post screening biopsies.
5. Screening laboratory test results within the following parameters (if 1 or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted during the approximately 4-week screening period):
a. White blood cells (WBCs) >=3.5 x 103/µL
b. Absolute neutrophil count (ANC) >=1.5 x 103/µL
c. Hemoglobin >= 10.0 g/dL
d. Platelets >=100 x 103/µL.
e. Total bilirubin <=1.5 times the upper limit of normal (ULN).
f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <=2 times the ULN
g. Creatinine clearance (calculated if measured is not available) >=60 mL/min/1.73m2
6. A woman must meet one of the following criteria:
o premenarchal;
o postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle-stimulating hormone [FSH] level >40 IU/L);
o permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy);
o otherwise incapable of pregnancy;
o have a negative pregnancy test result at screening and baseline.
7. Before randomization, a female subject of childbearing potential must be practicing a highly effective method of contraception and agrees to remain on a highly effective method while receiving study drug and until 12 weeks after last dose
8. Criterion modified per Amendment 4
8.1 A woman must agree not to breast feed, or to donate eggs (ova, oocytes) or freeze for future use, for the purposes of assisted reproduction during the study and for a period of 12 weeks after the last administration of study drug.
9. Criterion modified per Amendment 4

9.1 A man must agree not to father a child, or to donate sperm or freeze for future use, for the purposes of reproduction during the study and for a period of 12 weeks after the last administration of study drug.
10. Are considered eligible according to the following tuberculosis (TB) screening criteria:
a. Have no history of latent or active TB prior to screening.
b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
c. Have had no recent close contact with a person with active TB.
d. Within 8 weeks prior to the first administration of study intervention, have a negative QuantiFERON®-TB test result.
e. Have a chest x-ray (both posterior-anterior and lateral views, or per country regulations where applicable), taken <=12 weeks before the first administration of study intervention and read by a qualified radiologist, with no evidence of current, active TB or old,
inactive TB.
11. Sign an informed consent form.
12. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

Exclusion criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.
1. Prior use of any biologic therapy targeting IL-12/23, IL-17, or IL-23 receptor antagonists.
2. Criterion modified per Amendment 4: Use of non-steroidal anti-inflammatory drugs other than aspirin exceeding 5 days per month, unless completes a 4-week washout period prior to randomization. The use 100 mg of aspirin a day or 700 mg of aspirin per week is allowed.
3. Treatment with other FAP-directed drug therapy, unless completes a 4-week washout period prior to randomization.
Criterion modified per Amendment 3.
4.1 High grade dysplasia or cancer on biopsy at screening in GI tract (including stomach,
duodenum, and colon/rectum/pouch).
5. Criterion modified per Amendment 4.
5.2 Duodenal, colorectal, or pouch polyp:
• >2 cm unless excised at the screening evaluation.
• 1 to 2 cm with evidence of high-grade dysplasia upon biopsy unless excised.
6. Tests positive for hepatitis B virus (HBV) infection or is seropositive for antibodies to hepatitis C virus (HCV).
7. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection, recurrent urinary tract infection, or open, draining, or infected skin wounds

or ulcers.
8. Has current signs or symptoms of a clinically significant infection. Established non-serious infections need not be considered exclusionary at the discretion of the investigator.
9. Has a history of serious infection, including any infection requiring hospitalization or IV antibiotics, for 8 weeks before baseline.
10. Has evidence of a herpes zoster infection within 8 weeks before baseline.
11. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis. Participants with radiographic evidence of possible prior histoplasmosis or coccidioidomycosis will be excluded.
12. Has a chest x-ray within 12 weeks prior to the first administration of study intervention that shows an abnormality suggestive of a malignancy or current active infection, including TB.
13. Has or has had a nontuberculous mycobacterial infection or clinically significant opportunistic infection (eg, cytomegalovirus colitis, pneumocystosis, invasive aspergillosis).
14. History of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV.
15. Any serious underlying medical or psychiatric condition, dementia or altered mental status or any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or that in the opinion of the investigator would contraindicate the subject*s participation in the study or confound the results of the study.
16. History of severe, progressive, or uncontrolled renal, genitourinary, hepatic, hematologic, endocrine, cardiac, vascular, pulmonary, rheumatologic, neurologic, psychiatric, or metabolic disturbances, or signs and symptoms thereof.
17.Criterion modified per Amendment 4.: Received, or is expected to receive, any live virus or live bacterial vaccination within 12 weeks before the first administration of study intervention.
18. Has had a BCG vaccination within 12 months of screening
Criterion modified per Amendment 3.
19.1 Currently has a malignancy or has a history of malignancy within 5 years before
screening (with the exception of a nonmelanoma skin cancer that has been adequately
treated with no evidence of recurrence for at least 12 weeks before the first study
intervention administration or cervical carcinoma in situ that has been treated with no
evidence of recurrence for at least 12 weeks before the first study intervention administration or localized papillary thyroid carcinoma that has been treated with no
evidence of recurrence for at least 12 weeks before the first study intervention administration).
20. Has a known history of lymphoproliferative disease, including monoclonal

gammopathy of unknown significance, lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy, hepatomegaly, or splenomegaly, or monoclonal gammopathy of undetermined significance.
21. Has a transplanted organ (with exception of a corneal transplant >12 weeks before screening).
22. Known hypersensitivity, allergies, or intolerance to any excipient contained in the study drug (see guselkumab IB).
23. Has received an experimental antibody or biologic therapy within the previous 6 months, or received any other experimental therapy or new investigational agent within 30 days or 5 half-lives (whichever is longer) of any administration of study intervention or is currently enrolled in, or intends to participate in any other study using an investigational agent or procedure during participation in this study.
24. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
25. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	04-12-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	TREMFYA
Generic name:	Guselkumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-07-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-02-2022
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	EUCTR2019-001980-57-NL
ClinicalTrials.gov	NCT03649971
CCMO	NL70514.018.19

Study results

Date completed: 23-03-2022

Results posted: 19-09-2024

First publication
08-04-2023

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File