A MULTICENTRE, SAD, AND MAD CLINICAL TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF IV TREATMENT OF CALY-002 IN HEALTHY SUBJECTS AND SUBJECTS WITH COELIAC DISEASE AND EOSINOPHILIC OESOPHAGITIS

Published: 07-10-2020
Last updated: 17-01-2025

The objectives of Part B of the study are as follows: Primary: To assess the safety and tolerability of CALY-002 following multiple ascending doses administered IV in subjects with coeliac disease (CeD). Secondary: (1) To characterise the PK of CALY…

Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal conditions NEC
Study type	Interventional

Summary

ID

NL-OMON52682

Source
ToetsingOnline

Brief title
CALY-CL19-001

Condition

- Gastrointestinal conditions NEC

Synonym
Allergic esophagus inflammation, Coeliac disease, Gluten intolerance; Eosinophilic

oesophagitis

Research involving
Human

Sponsors and support

Primary sponsor: Calypso Biotech BV
Source(s) of monetary or material Support: Calypso Biotech BV

Intervention

Keyword: CALY-002, Coeliac disease, Eosinophilic oesophagitis, Healthy volunteers

Outcome measures

Primary outcome

Part B:

Primary: To assess the safety and tolerability of CALY-002 following multiple

ascending doses administered IV in subjects with coeliac disease (CeD).

Part C:

Primary: To assess the safety and tolerability of CALY-002 following multiple

IV administration in subjects with eosinophilic oesophagitis (EoE).

Secondary outcome

Part B:

Secondary:

(1) To characterise the PK of CALY-002 following multiple ascending doses

administered IV in subjects with CeD;

(2) To investigate the immunogenicity of CALY-002 following multiple ascending

doses administered IV in subjects with CeD.

Part C:

Secondary:

(1) To characterise the PK of CALY-002 following multiple IV administration in

subjects with EoE;

(2) To investigate the immunogenicity of CALY-002 following multiple IV

administration in subjects with EoE.

Study description

Background summary

The current study is evaluating the use of CALY-002, which is being developed for the treatment of celiac disease (CeD) and eosinophilic esophagitis (EoE)

A gluten-free diet (GFD) is the only effective treatment for CeD, as there are currently no medications that can reliably and safely prevent the mucosal damage caused by exposure to gluten (Rubio-Tapia 2013).
Strict avoidance of gluten is also difficult because there are many hidden sources of gluten in commercial food products, cosmetics, and drugs.
Therefore, there is a clear unmet medical need for new, safe, and efficacious treatments for CeD and refractory CeD.

Treatment options for EoE include dietary interventions or swallowed corticosteroids, which have resulted in varying levels of success in patients; this variation suggests a degree of heterogeneity in the disease.
In January 2018, budesonide administered as orodispersible tablets was approved for the treatment of patients with EoE in Europe (Jorveza® 2019). However, side effects such as oropharyngeal candidiasis occur, some patients
do not respond, and the use of corticosteroids for an indeterminate time is not appropriate for many patients. Therefore, there still remains an unmet medical need to develop new, safe, and efficacious treatments for EoE.

Study objective

The objectives of Part B of the study are as follows:
Primary: To assess the safety and tolerability of CALY-002 following multiple ascending doses administered IV in subjects with coeliac disease (CeD).

Secondary:

(1) To characterise the PK of CALY-002 following multiple ascending doses administered IV in subjects with CeD;
(2) To investigate the immunogenicity of CALY-002 following multiple ascending doses administered IV in subjects with CeD.

Exploratory:
(1) To characterise the potential blood and tissue biomarkers (PD) of CALY-002 following multiple ascending doses administered IV in subjects with CeD;
(2) To determine the preliminary efficacy of CALY-002 following multiple ascending doses administered IV in subjects with CeD.

The objectives of Part C of the study are as follows:
Primary: To assess the safety and tolerability of CALY-002 following multiple IV administration in subjects with eosinophilic oesophagitis (EoE).

Secondary:
(1) To characterise the PK of CALY-002 following multiple IV administration in subjects with EoE;
(2) To investigate the immunogenicity of CALY-002 following multiple IV administration in subjects with EoE.

Exploratory:
(1) To characterise the potential blood and tissue biomarkers (PD) of CALY-002 following multiple IV administration in subjects with EoE;
(2) To determine the preliminary efficacy of CALY-002 following multiple IV administration in subjects with EoE.

Study design

Part B is a multicentre, randomised, double-blind, placebo-controlled, multiple ascending dose (MAD) study to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of CALY-002 administered IV to subjects with CeD who undergo a concurrent 8-week gluten challenge.

Part B will consist of multiple ascending doses of IV CALY-002 in up to three sequential cohorts (two dose escalation cohorts [Cohorts B1 and B2] and one optional cohort [Cohort B3/Enrichment Cohort]). Each cohort will consist of 9 subjects; 6 subjects will receive CALY-002 and 3 subjects will receive placebo, according to the randomisation schedule. A blocking scheme of size 3 (2:1 CALY-002: placebo) will be prepared for the randomisation schedule.

The total duration of the study for each subject enrolled in Part B will be up to 27 weeks and will include the following: Screening Period (up to 56 days; Days -56 to -1), Treatment Period (8 weeks; dosing on Days 1, 15, 29, and 43; Day 57 will mark the end of the 8-week Treatment Period), and Follow-up Period (Days 73 and 133). Day 133 will be the Final Follow-up/EOS Visit. All study visits in Part B will be performed on an out-patient basis.

Part C (multiple dosing) is a multicentre, open-label, multi-cohort study consisting of 8 to 12 subjects with EoE. The maximally 3 cohorts consist of 4 subjects each. Subjects will receive IV administration of CALY-002 at a currently planned dose of 210 mg q2w for 12 weeks (3 × 28-day treatment cycles; a total of 6 study drug administrations). in the first cohort of 4 subjects, i.e., Cohort C1, and a planned maximum
of 700 mg q2w for 12 weeks in the second cohort of 4 subjects (Cohort C2); the study can be expanded to 12 subjects by adding a third cohort of 4 subjects; Cohort C3. Placebo will not be administered to subjects in this cohort; therefore, the treatment assignment will be open label.

The total duration of the study for each subject enrolled in Part C will be up to 29 weeks and will include the following: Screening Period (up to 42 days; Days -42 to -1), Treatment Period (12 weeks; dosing on Days 1, 15, 29, 43, 57, and 71; Day 85 will mark the end of 12-week Treatment Period), and Follow-up Period (Days 101 and 161). Day 161 will be the Final Follow-up/EOS Visit. All study visits in Part C will be performed on an out-patient basis.

Intervention

Subjects in Cohorts B1 (70 mg dose) and B2 (210 mg dose) will receive the study drug (CALY-002 or placebo) IV once every 2 weeks (q2w) for 8 weeks (2 × 28-day treatment cycles; a total of 4 doses).

All subjects in cohort C1 will receive IV administration of CALY-002 at a currently planned dose of 210 mg q2w for 12 weeks (3 × 28-day treatment cycles; a total of 6 study drug administrations).

Study burden and risks

Treatment with study drug
This will be the first time that the study drug will be given in multiple administrations to patients with coeliac disease. Therefore, information about all the risks or side effects that may occur is not yet known.
As with any new substance, new, unforeseeable and unknown adverse events (site effects) could arise. These adverse events could be serious, life threatening/deadly or even cause long-term damage. You may be the first person to experience an unknown side effect. Therefore, it is very important that you inform the study team about any new symptom you might have.

As with the intake of any other foreign substance (or any other drug) an allergic reaction may occur. Possible symptoms are e.g. a rash, itching, swelling in the face or throat, breathing difficulties, decreased blood pressure, accelerated pulse and sudden sweating or cold sweat. If these symptoms occur soon after the administration of a substance and are very severe, this is called a potentially life-threatening anaphylactic reaction

that needs immediate medical attention.

When the substance was intravenously administered to cynomolgus monkeys at very high doses (up to 75 mg/kg body weight weekly) over a period of 13 weeks, it showed that CALY-002 was well tolerated and no allergic reactions nor adverse events were observed. Nevertheless, due to the differences between humans and the animal species tested so far, it is not possible to make a reliable statement on how the test substance works in humans.

Based on the general characteristics of the study drug, the safety and toxicology data generated in animal studies and the administration of the study drug as a 1 hour-infusion, the following potential risks have been identified for the treatment with CALY-002:
• Allergic reaction
• Potential reactivation of a previous Herpes zoster (also called shingles) infection

Any side effect should be reported to the study doctor or study team, particularly if it occurs at home or outside the hospital before the final study visit (End of study visit) on Day 133.

Gluten consumption
You may experience the same symptoms that you have when you accidentally ingest gluten. However, it is not clear how severe your symptoms might become over the course of the gluten consumption. The amount of daily gluten intake is chosen to be low enough to not provoke severe symptoms that make you feel sick. Some people see a return of their symptoms almost immediately (within a day or two) and continue to have symptoms as long as they eat gluten, whereas some people may feel more discomfort early in the gluten consumption period but then don*t notice too many symptoms as they continue to eat gluten. Others might not notice any symptoms at all from their gluten consumption.
It is possible (in very rare cases) that your overall health may deteriorate over the course of the gluten consumption. All symptoms related to the gluten intake are expected to resolve once the study Treatment Period is finished and you comply with your strict gluten free diet. During the study you should not consume more gluten than provided as part of the study (e.g. the gluten cookies) since you do have coeliac disease and would risk further complications if you did.

You may also experience other unwanted effects or discomforts with the study procedures.

Contacts

Public
Calypso Biotech BV

Gustav Mahlerplein 102
Amsterdam 1082 MA
NL
Scientific
Calypso Biotech BV

Gustav Mahlerplein 102
Amsterdam 1082 MA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

For inclusion in Part B of the study, a subject with CeD should meet all of the following criteria:
1. Subject is a male or female >= 18 years of age, at the time of signing the ICF.
2. Subject has a BMI between > 17.5 and < 35.0 kg/m2 (both inclusive).
3. Subject must be willing to consent to all study-related procedures and visits, including a minimum of 2 endoscopy procedures with small intestine biopsies during study participation. Subject must have signed an ICF indicating that he/she understands the purpose of and procedures required for the study and is willing to participate in the study.
4. Subject must have a diagnosis of CeD by intestinal biopsy at least 12 months prior to screening as confirmed by medical records.
5. Subject must have no histological signs of active CeD at screening as confirmed by a screening intestinal biopsy, with a VH:CD ratio > 1.5 and CD3+ IEL density < 40 cells/100 villus enterocytes.
6. Subject must have been on a GFD for at least 12 consecutive months prior to

screening and will have to remain on a GFD for the duration of study participation (during the 8-week gluten challenge, subjects will consume approximately 3 g of gluten daily while continuing with their GFD).
7. Subject must have negative anti-tissue transglutaminase (tTG) immunoglobulin A (IgA) serology at screening. Note: At primary diagnosis of CeD, subjects should have had a Marsh score of at least IIIA/B/C and either the existence of positive TG-IgA serology that became negative upon GFD or clinical improvement after introduction of GFD. If no TG-IgA serology was done at the first diagnosis, then the investigator should contact the medical monitor and discuss subject eligibility.
8. Subject must have human leukocyte antigen (HLA) genotype DQ2 or DQ8 as confirmed by medical records.
9. Subject must be willing to undertake a gluten challenge (ie, intake of approximately 3 g of gluten daily) for 56 consecutive days (8 weeks) during the Treatment Period. Note: This will be the only allowed intake of gluten while subjects need to remain on their GFD throughout study participation.
10. Subject must be healthy on the basis of physical examination findings, clinical laboratory tests, medical history, vital signs, and cardiac monitoring (normal 12-lead ECG results) performed at screening, in the opinion of the investigator.
11. An FCBP must either commit to true abstinence from heterosexual contact or agree to use, and be able to comply with, at least two effective contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation or intrauterine device; barrier contraceptive with spermicide; or vasectomised partner), one of which must be a barrier method, from the time of signing the ICF through EOS. In addition, an FCBP must have two negative pregnancy tests as verified by the investigator prior to receiving the first dose:
• A negative serum FSH and β-HCG pregnancy test at screening.
• A negative urine pregnancy test prior to randomisation on Day 1.
12. A male subject must practice true abstinence or agree to use a condom (a latex condom is recommended) during sexual contact with a pregnant female or an FCBP and will avoid conceiving from the time of signing the ICF through EOS, even if he has undergone a successful vasectomy.
13. Subject has a negative COVID-19 test within 48 hours prior to Day 1.

For inclusion in Part C of the study, a subject with EoE should meet all of the following criteria:
1. Subject is a male or female >= 18 years of age, at the time of signing the ICF.
2. Subject has a BMI between > 17.5 and < 35.0 kg/m2 (both inclusive).
3. Subject must be willing to consent to all study-related procedures and visits, including a minimum of 2 endoscopy procedures with oesophageal biopsies during study participation. Subject must have signed an ICF indicating that he/she understands the purpose of and procedures required for the study and is willing to participate in the study.
4. Subject must have endoscopically confirmed and documented diagnosis of EoE,

with active eosinophilia on oesophageal biopsy showing a peak eosinophil count of >= 15 eosinophils/high power field (eos/hpf) at least 1 oesophageal level.
5. Subject should exhibit active symptoms of dysphagia with more than 3 episodes of dysphagia during a period of 2 weeks during screening.
6. Subject must have clinically active disease with a Straumann Dysphagia Instrument (SDI) patient-reported outcome (PRO) score >= 5 at screening and Day 1/baseline prior to the first dose (Straumann 2010).
7. Subject must have had a relapsed EoE or did not respond after first-line therapy (elimination diet, proton-pump inhibitor [PPI], corticosteroid) according to EoE guideline (Lucendo 2017). If the subject received prior treatment with a PPI, then he/she must have had failed to respond to at least 8 weeks of recommended daily dosing (ie, a total daily dose of >= 40 mg) with PPI per EoE guideline (Lucendo 2017).
8. Subject must be healthy on the basis of physical examination findings, clinical laboratory tests, medical history, vital signs, and cardiac monitoring (normal 12-lead ECG results) performed at screening, in the opinion of the investigator.
9. An FCBP must either commit to true abstinence from heterosexual contact or agree to use, and be able to comply with, at least two effective contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation or intrauterine device; barrier contraceptive with spermicide; or vasectomised partner), one of which must be a barrier method, from the time of signing the ICF through EOS. In addition, an FCBP must have two negative pregnancy tests as verified by the investigator prior to receiving the first dose:
• A negative serum FSH and β-HCG pregnancy test at screening.
• A negative urine pregnancy test prior to the first dose on Day 1.
10. A male subject must practice true abstinence or agree to use a condom (a latex condom is recommended) during sexual contact with a pregnant female or an FCBP and will avoid conceiving from the time of signing the ICF through EOS, even if he has undergone a successful vasectomy.
11. Subject has a negative COVID-19 test within 48 hours prior to Day 1.

Exclusion criteria

A subject with CeD will not be eligible for inclusion in Part B of this study if any of the following criteria apply:
1. Subject has a concurrent active autoimmune disease (other than CeD) that requires systematic treatment with immunosuppressants. Note: Inclusion of subjects with a history of autoimmune disease without symptoms or treatment for more than 3 years or subjects with autoimmune thyroiditis that is well controlled with levothyroxine substitutions can be discussed with the medical monitor.
2. Subject has severe complication of CeD such as refractory CeD.
3. Subject has active dermatitis herpetiformis.

4. Subject has active (microscopic) colitis with clinical signs of diarrhoea and abdominal pain.
5. Subject has any significant medical condition (including but not limited to neurological, gastrointestinal, renal, hepatic, cardiovascular, psychological, pulmonary, metabolic, endocrine, haematological, drug allergies, or other major disorders), laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
6. Subject has any condition that confounds the ability to interpret data from the study.
7. Subject is pregnant or breastfeeding.
8. Subject is currently receiving or has been previously treated with a biologic agent. Exception: If prior treatment with the biologic agent was completed at least 6 months prior to the first dose, the medical monitor can be consulted for potential recruitment.
9. Subject has a history of anaphylactic reactions to protein therapeutics.
10. Subject has evidence of SARS-CoV-2 infection and/or subject has not been fully vaccinated for COVID-19 (according to the vaccine's local summary of product characteristics) at least 2 weeks before screening and/or subject is deemed at risk for the coronavirus disease (COVID19) in the opinion of the treating physician or the subject has participated in another clinical study involving treatment(s), which may increase such risk.
11. Subject has participated or is planning to participate in another investigational drug study within 60 days prior to the first dose.
12. Subject has malignancy or prior malignancy, with a disease free interval of < 5 years after diagnosis and intervention, except for curative treatment for non-melanoma skin cancer or resected carcinoma in situ.
13. Subject has current or recent (within 4 weeks prior to screening) signs or symptoms of infection that require parenteral antibiotic administration.
14. Subjects has a hepatitis B infection (confirmed by HBsAg), hepatitis C infection (confirmed by HCV RNA testing), or HIV 1 or HIV-2 antibodies or infection at screening.
15. Subject has had major surgery (including joint surgery) within 8 weeks prior to screening and hospitalisation for a clinically relevant event within the 4 weeks prior to screening.
16. Subject has received immunisation with a live or live attenuated vaccine within 60 days prior to the first dose or is planning to receive immunisation with a live or live attenuated vaccine within 60 days after the last dose.
17. Subject has been committed to an institution by way of official or judicial order.
18. Subject has used any new prescription or experimental drugs (including biologics/monoclonal antibodies) for the treatment of their coeliac disease 30 days or 5 half-lives, whichever is shorter prior to randomisation. Note: Changes in the concomitant medication must be reviewed by the investigator and the medical monitor and prior to starting any new concomitant medication (prescription or over-the-counter) during the study treatment period, the investigator must be informed and the prescription must be reviewed and approved by the investigator and the medical monitor.

19. Subject has current or recent (i.e., within 4 weeks prior to screening) abdominal pain, diarrhea, or other gastroenterological signs or symptoms that may hamper the evaluation of signs and symptoms that possibly are elicited by the gluten challenge during the study.
20. Subject has a liver function abnormality reflected as AST or ALT >2 times the upper limit of normal and/or total bilirubin >1.5 times the upper limit of normal.

A subject with EoE will not be eligible for inclusion in Part C of this study if any of the following criteria apply:
1. Subject has a hyper-eosinophilic syndrome. Note: At screening, subjects will be screened for signs of eosinophilic gastritis, duodenitis, or colitis to confirm limited EoE and rule out eosinophilic syndrome.
2. Subject has a concurrent active autoimmune disease (other than EoE) that requires systematic treatment with immunosuppressants. Note: Inclusion of subjects with a history of autoimmune disease without symptoms or treatment for more than 3 years or subjects with autoimmune thyroiditis that is well controlled with levothyroxine substitutions can be discussed with the medical monitor.
3. Subject has active (microscopic) colitis with clinical signs of diarrhoea and abdominal pain.
4. Subject has any significant medical condition (including but not limited to neurological, gastrointestinal, renal, hepatic, cardiovascular, psychological, pulmonary, metabolic, endocrine, haematological, drug allergies, or other major disorders), laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
5. Subject has any condition that confounds the ability to interpret data from the study.
6. Subject is pregnant or breastfeeding.
7. Subject is currently receiving or has been previously treated with a biologic agent. Exception: If prior treatment with the biologic agent was completed at least 6 months prior to the first dose, the medical monitor can be consulted for potential recruitment.
8. Subject has a history of anaphylactic reactions to protein therapeutics.
9. Subject has evidence of SARS-CoV-2 infection and/or subject has not been fully vaccinated for COVID-19 (according to the vaccine*s local summary of product characteristics) at least 2 weeks before screening and/or subject is deemed at risk for the coronavirus disease (COVID-19) in the opinion of the treating physician or the subject has participated in another clinical study involving treatment(s), which may increase such risk.
10. Subject has participated or is planning to participate in another investigational drug study within 60 days prior to the first dose.
11. Subject has malignancy or prior malignancy, with a disease free interval of < 5 years after diagnosis and intervention, except for curative treatment for non-melanoma skin cancer or resected carcinoma in situ.
12. Subject has current or recent (within 4 weeks prior to screening) signs or symptoms of infection that require parenteral antibiotic administration.

13. Subjects has a hepatitis B infection (confirmed by HBsAg), hepatitis C infection (confirmed by HCV RNA testing), or HIV-1 or HIV-2 antibodies or infection at screening.
14. Subject has had major surgery (including joint surgery) within 8 weeks prior to screening and hospitalisation for a clinically relevant event within the 4 weeks prior to screening.
15. Subject has received immunisation with a live or live attenuated vaccine within 60 days prior to the first dose or is planning to receive immunisation with a live or live attenuated vaccine for 60 days after the last dose.
16. Subject has been committed to an institution by way of official or judicial order.
17. Subject has used any new prescription or experimental drugs (including biologics/monoclonal antibodies) for the treatment of their coeliac disease 30 days or 5 half-lives, whichever is shorter prior to randomisation. Note: Changes in the concomitant medication must be reviewed by the investigator and the medical monitor and prior to starting any new concomitant medication (prescription or over-the-counter) during the study treatment period, the investigator must be info

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	05-10-2021
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CALY-002
Generic name:	-

Ethics review

Approved WMO Date:	07-10-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-12-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	10-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2020-000726-25-NL
CCMO	NL74371.056.20

Study results

Date completed: 02-04-2024

Results posted: 02-10-2024

First publication
27-08-2024