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ABO809

Clinical Trial Protocol CABO809A02101

An Open Label *Cryptosporidium* Controlled Human Infection Model (CHIM) to assess the efficacy and safety of ABO809 in healthy participants

Document type:	Amended Protocol Version
EUDRACT number:	N/A
Version number:	v02 (Clean)
Clinical Trial Phase:	I
Release date:	02-Dec-2021

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Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020

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List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
bpm	Beats Per Minute
BUN	Blood Urea Nitrogen
CDC	Centers for Disease Control and Prevention
CE	*C. parvum* oocysts
Center No.	Center Number
CFR	U.S. Code of Federal Regulations
CHIM	Controlled Human Infection Model
CLIA	Clinical Laboratory Improvement Amendments
CMO&PS	Chief Medical Office and Patient Safety
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report

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DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Record/Report Form
EDC	Electronic Data Capture
EIA	Enzyme immunoassay (detects *Cryptosporidium* specific antigens in stool samples)
EMA	European Medicines Agency
EOS	End of Study
eSource	Electronic Source
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice

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HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCP	Healthcare Provider
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form

ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID50	Median Infectious Dose
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IN	Investigator Notification
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine System
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
n	Number
OTC	Over The Counter
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
PT	Prothrombin Time
QMS	Quality Management System

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QTcF	QT interval corrected by Fridericia's formula
RBC	Red Blood Cell(s)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SI	International System of Units
SUSAR	Suspected Unexpected Serious Adverse Reaction
THC	Tetrahydrocannabinol
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
USPI	US-Package Insert
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience, or characteristic, or a group of individuals followed up or traced over time.
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants.
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient). “Participant” terminology is used in the protocol whereas “Subject” is used in data collection

Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Tele-visit	Procedures or communications conducted using technology such as telephone or videoconference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.

Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

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IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Protocol summary

Protocol number	CABO809A02101
Full Title	An Open Label *Cryptosporidium* Controlled Human Infection Model (CHIM) to assess the efficacy and safety of ABO809 in healthy participants.
Brief title	Study of efficacy and safety of ABO809 in healthy participants.
Sponsor and Clinical Phase	Novartis Phase I study
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The goal of this Phase I CHIM study is to determine if oral administration of a GMP supply of *Cryptosporidium parvum* oocysts (ABO809) to healthy volunteers results in *Cryptosporidium* infection and diarrheal illness. The study will measure fecal *Cryptosporidium* oocysts (parasitological endpoint) as well as diarrhea and associated signs and symptoms (clinical endpoint). A similar CHIM model would be used in future studies to evaluate the efficacy of novel therapies and vaccines for the treatment and prevention of *Cryptosporidium* infection in healthy participants before they are assessed in the pediatric target population.
Primary Objective(s)	The primary objective of this study is to evaluate the incidence of *Cryptosporidium* infection following an oral administration of ABO809.
Secondary Objectives	The secondary objectives of this study are to evaluate the incidence and characteristics of diarrheal illness following an oral administration of ABO809, to evaluate the time to onset and resolution of *Cryptosporidium* infection in participants who developed an infection following administration of an oral ABO809 administration, and to assess the safety and tolerability of ABO809.
Study design	The study will consist of up to a 28-day Screening/Baseline period, after which a single dose of ABO809 will be administered to all participants. This will be followed by a 10-day inpatient monitoring period, an outpatient follow-up period, and a study completion visit on Day 56. Following the Day 56 visit, there will be a Post-Study Follow-Up call conducted at 6 months and 12 months. Participants who develop a *Cryptosporidium* infection, with or without clinical symptoms, will receive a standard 3-day course of nitazoxanide treatment per the U.S. Prescribing Information on Day 21. A total of up to 6 sequential cohorts of approximately 10 participants each will be enrolled.
Study population	Up to approximately 60 healthy male and female participants between 18 to 50 years of age without a history of *Cryptosporidium* infection will be enrolled in this study.
Key Inclusion criteria	Key inclusion criteria include demonstrated understanding of *Cryptosporidium* disease, safety measures and transmission risks, good health, and ability to communicate well with the Investigator.
Key Exclusion criteria	Key exclusion criteria are history of *Cryptosporidium* infection, gastrointestinal conditions (including diarrheal syndromes, gastroenteritis and gastrointestinal tract surgery), immunodeficiency, infections, significant medical concerns, hypersensitivity to nitazoxanide or other specified antibiotics.

ABO809 administration	GMP *Cryptosporidium parvum* oocysts (ABO809) administered orally.
Treatment of interest	There is no "Treatment of interest" per se since this study aims to establish a human controlled infection model for cryptosporidiosis. In this protocol, we consider ABO809 as the “Intervention of interest” instead.
Efficacy assessments	The primary endpoint is the number of participants with *Cryptosporidium* infection (presence of fecal oocysts) ≥72 hours following administration of an oral administration of ABO809 (or sooner if associated with symptoms suggestive of diarrheal illness). Secondary endpoints include characterization of diarrheal illness, safety and tolerability.
Key safety assessments	Safety assessments will include vital signs, ECG, safety laboratory assessments, AEs and SAEs.
Other assessments	Commercially Confidential Information
Data analysis	The number and proportion (in percentage) of participants with *Cryptosporidium* infection will be summarized. The 1-sided 80% exact confidence interval with a lower limit of the proportions will also be reported. In addition, the number and proportion of participants with diarrheal illness will be reported in the same fashion.
Key words	Controlled Human Infection Model, CHIM, infection, diarrhea, safety, tolerability, healthy volunteers, Phase I, cryptosporidiosis, *Cryptosporidium*, oral, ABO809

1 Introduction

1.1 Background

Recent studies have found *Cryptosporidium* infections to be a leading cause of pediatric diarrhea worldwide (Kotloff et al 2013, Platts-Mills et al 2015). In certain vulnerable populations, the infection is protracted and potentially life threatening, including young children (i.e., aged 0-2), malnourished children of any age, and immunocompromised individuals (e.g., those with HIV/AIDS). Furthermore, repeated *Cryptosporidium* infections in children are associated with long-term and debilitating growth-stunting as well as impairment in cognitive development (Guerrant et al 2013, Checkley et al 1998, Platts-Mills et al 2015). In children, even asymptomatic infections are associated with growth deficits (Checkley et al 1997). In addition, cryptosporidiosis remains a common cause of chronic diarrhea in HIV/AIDS patients in developing countries (Panel on Opportunistic Infections 2018).

Cryptosporidium species (spp.) are protozoan parasites responsible for enteritis with watery diarrhea as the primary clinical symptom. Cryptosporidiosis in humans is caused primarily by two species, *Cryptosporidium hominis* and *Cryptosporidium parvum* (Checkley et al 2015). Transmission typically occurs when feces containing *Cryptosporidium* oocysts from infected animals/humans contaminate food and water supplies, thereby infecting humans via the fecal-oral route. Once ingested, the oocysts reach the small intestine where motile, infectious sporozoites are released from the oocysts and infect intestinal epithelial cells. The organism typically then goes through multiple cycles of asexual followed by sexual reproduction, ultimately resulting in excretion of numerous mature oocysts in the feces. Individuals may shed 10^8-10^9 oocysts during an infection period and may excrete oocysts for up to 50 days after resolution of diarrhea (Putignani and Menichella 2010).

Cryptosporidiosis typically is a self-limiting infection in immunocompetent adults. Following infection, healthy, immunocompetent individuals may experience profuse, watery, non-bloody diarrhea after an incubation period of 3-12 days (Chappell et al 1999). Acute watery diarrhea as the cardinal symptom of cryptosporidiosis has been described to last approximately 2 weeks (Chen et al 2002), but can persist for longer (Mac Kenzie et al 1994). Other symptoms can include weight loss, abdominal pain, anorexia, fatigue, cramps, headache, fever, and vomiting (Painter et al 2015). Some healthy individuals may remain asymptomatic after exposure. In this Controlled Human Infection Model (CHIM) study, *Cryptosporidium parvum* will be used. Post-infectious irritable bowel syndrome has been described in patients with enteritis due to bacterial pathogens such as *Campylobacter*, *Salmonella* or *Shigella (*Ozgül et al 1999). Seronegative reactive arthritis, including Reiter's syndrome, and relapse in Crohn's disease and ulcerative colitis have also been reported (Cron and Sherry 1995, Colussi et al 2010). In one study, persistent gastrointestinal symptoms were reported up to 25-36 months post-infection (Insulander et al 2013). Interpretation of self-reported data from outbreak-associated cohorts requires caution given the potential for bias towards those most adversely affected and those who attributed post-acute symptoms to acute cryptosporidiosis. Long-term sequelae have not been described in CHIM studies.

Currently, nitazoxanide (Alinia®) is the only drug approved by the United States Food and Drug Administration for the treatment of cryptosporidiosis. The drug is indicated for treatment of diarrhea caused by *C. parvum* in patients 1 year of age and older. However, nitazoxanide has not been shown to be effective for the treatment of diarrhea caused by *C. parvum* in HIV-infected or immunodeficient patients (Romark 2017). As the global competitive drug discovery landscape in cryptosporidiosis is sparse, there is an urgent need to identify new compounds that directly inhibit *Cryptosporidium*.

The goal of this study is to develop a method for establishing a reproducible and controlled *Cryptosporidium* infection in healthy adults that temporarily results in symptoms of cryptosporidiosis and is expected to resolve naturally within approximately 7-21 days. A healthy volunteer CHIM study is expected to allow for a careful, early examination of the pharmacokinetic-pharmacodynamic (PK-PD) relationship of a future investigational drug in a controlled setting, providing valuable data that informs future trial designs (Darton et al 2015, Pollard et al 2012). In contrast to real-world settings, participants in a cryptosporidiosis CHIM will have diarrhea due to a single pathogen, not potentially multiple ones. This will allow for unbiased interrogation of the effect of an investigational drug on clinical and parasitological endpoints. The safety and feasibility of controlled human *Cryptosporidium parvum* studies are well documented in the literature (Chappell et al 2006, DuPont et al 1995, Okhuysen et al 1999). If successful, this CHIM methodology would be used in the future (with different study participants) to enable assessment of novel therapies and vaccines for the treatment and prevention of cryptosporidiosis. A *Cryptosporidium* CHIM will provide important data demonstrating the prospect of benefit and informing dose selection of new therapies and vaccines before they are tested in vulnerable pediatric populations.

1.2 Purpose

The goal of this Phase I CHIM study will be to determine if oral administration of a Good Manufacturing Practice (GMP) supply of *C. parvum* oocysts (ABO809) to healthy volunteers results in *Cryptosporidium* infection and diarrheal illness. The study will measure fecal *Cryptosporidium* oocysts (parasitological endpoint) as well as diarrhea and associated signs and symptoms (clinical endpoint).

It is expected that approximately 90-100 percent of participants receiving ABO809 may become infected. The incidence of diarrheal illness will also be evaluated and may be somewhat lower than the incidence of infection.

This study, if successful, would enable a robust CHIM model that can be used in future studies to evaluate the efficacy of novel therapies and vaccines for the treatment and prevention of *Cryptosporidium* infection in healthy participants before they are assessed in the pediatric target population.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the incidence of *Cryptosporidium* infection following an oral administration of ABO809	• *Cryptosporidium* infection as indicated by *Cryptosporidium* oocysts in fecal samples measured by EIA CCI at ≥72 hours post-administration (or sooner if associated with symptoms of diarrheal illness) up to Day 10 (inclusive).
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the incidence and characteristics of diarrheal illness following an oral administration of ABO809	• Presence of clinical diarrheal illness by Day 10 (inclusive) and Day 28 • Number of diarrhea episodes • Stool weight • Grading of stool consistency • Time to onset and time to resolution of diarrheal illness • Characteristics of clinical signs and symptoms associated with clinical diarrheal illness such as (abdominal pain, abdominal cramping, nausea, vomiting, fever, electrolyte imbalance, dehydration) up to Day 28 • *Cryptosporidium* infection as indicated by *Cryptosporidium* oocysts in fecal samples measured by EIA CCI at ≥72 hours post-administration (or sooner if associated with symptoms of diarrheal illness up to Day 28)
• To evaluate the time to onset and resolution of *Cryptosporidium* infection in participants who developed an infection following an oral administration of ABO809	• Detection of fecal shedding of *C. parvum* oocysts by EIA CCI up to 28 days after administration of ABO809 • Time to onset and time to resolution of *Cryptosporidium* infection following an oral administration of ABO809
• To assess the safety and tolerability of ABO809	• Adverse events, vital signs, ECG findings, safety laboratory assessments including chemistry, hematology, and urinalysis results up to and including the Day 28 visit • Adverse events of special interest by telephone follow-up after Day 28 through 12 months after ABO809 administration
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

Objective(s)	Endpoint(s)
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3 Study design

This Phase 1 *Cryptosporidium* CHIM study employs a single-center, open-label design to characterize the incidence of infection and associated symptoms following the administration of single doses of *C. parvum* oocysts (ABO809).

The study will enroll healthy volunteers in cohorts of approximately 10 participants who will receive ABO809 on the same day. A dose level group will receive the same ABO809 dose and can be comprised of multiple cohorts. The first dose level group will start with a cohort of 10 participants who will receive ABO809 at a dose of $1x10^4$ oocysts. The study will continue to enroll participants in the same dose level group if the desired incidences of infection and diarrheal illness are observed, up to a total of approximately 30 participants. If the desired incidences of infection and diarrheal illness are not observed, a new dose level group, receiving ABO809 at a dose of $1x10^6$ oocysts, may be initiated. If needed to optimize the model, intermediate ABO809 doses may be evaluated (see Section 6.5).

The study will consist of three (to a maximum of six) sequential cohorts of approximately 10 participants each. The cohorts will be dosed one after the other for a total of 30 (to a maximum of approximately 60) participants. This is an adaptive study and for a particular cohort, safety, incidence of infection and incidence of clinical illness will be evaluated on Day 14 to inform whether the ABO809 dose needs to be changed for dosing of the next cohort (see Section 6.5.1). If there are no safety issues, and the expected incidence of infection and illness are observed in one cohort, the next cohort will be dosed at the same dose level (see Section 6.5.1 for details). If the dose of ABO809 is changed from one cohort to the next, additional cohorts may be added to further evaluate *Cryptosporidium* infection and clinical illness following dosing with ABO809.

The study will consist of up to a 28-day Screening/Baseline period, an ABO809 administration and inpatient monitoring period, an outpatient follow-up period, and a study completion evaluation on Day 56. Additionally, Post-Study Follow-Up Calls will be conducted at 6 and 12 months after ABO809 administration. A CHIM diary will be provided to each participant to collect information on the participant's clinical symptoms.

Participants will receive a single oral dose of ABO809 on Day 1.

Cryptosporidium infection is defined as the presence of oocysts in at least 1 stool sample starting 72 hours following the administration of ABO809 (or sooner if associated with symptoms suggestive of diarrheal illness) and up to Day 10.

If clinical symptoms associated with cryptosporidiosis occur earlier than 72 hours post-administration, then stool samples after the onset of symptoms can be collected for parasitological evaluation for the primary endpoint. Normal bowel transit time varies from 30 to 40 hours, and therefore ≥72 hours is chosen to minimize the chance of detecting only passively excreted oocysts given orally.

Resolution of *Cryptosporidium* infection is defined as no evidence of *Cryptosporidium* in stool samples collected over ≥2 consecutive days.

Stool samples will also be collected and sent to the laboratory in instances of relapse symptoms suggestive of *Cryptosporidium* infection until Day 28. Participants experiencing diarrheal symptoms between Day 28 and Day 56 may return for an unscheduled visit and provide stool for assessment of *Cryptosporidium* infection.

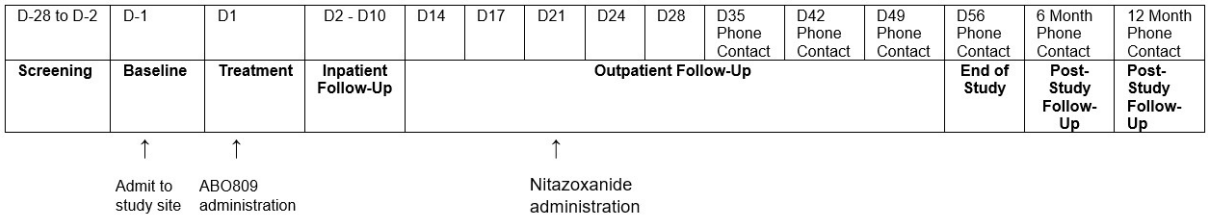
A participant will be considered as showing clinical diarrheal illness if diarrhea is observed with at least two diarrheal bowel events within 24 hours on at least two days during the observation period beginning after the ABO809 administration (Day 1) and ending on Day 28 (see Section 8.3.2)

Resolution of diarrheal illness from *Cryptosporidium* infection requires ≥2 consecutive days with no diarrheal stools (stool sample grades 1 or 2).

Participants will be monitored daily for infection (parasitological evaluation) and diarrheal illness (clinical evaluation) during the domicile period. The monitoring of symptoms will continue in the outpatient setting with the collection of information via the CHIM diary and Safety Follow-Up Calls. Participants will provide a health and stool update daily from Day 1 through 28 in the CHIM diary. Safety Follow-Up Calls will occur on Days 35, 42, 49, and 56.

The primary endpoint is *Cryptosporidium* infection as indicated by detection of oocysts in fecal samples by EIA CCI ≥72 hours following an oral administration of ABO809 (or sooner if associated with symptoms suggestive of diarrheal illness). Secondary endpoints include characterization of diarrheal illness, safety and tolerability.

Figure 3-1 Study Design



3.1 Screening/Baseline Period

After written informed consent has been obtained, healthy participants 18 to 50 years of age will be enrolled and educated about *Cryptosporidium* and its potential effects in humans. Following the provision of consent, volunteers will then take a written quiz to ascertain their level of understanding about the characteristics of *Cryptosporidium* infection, its transmission and appropriate safety precautions to avoid secondary infection. Participants who score 100% on the quiz and meet the eligibility criteria at Screening can advance in the study to receive one dose of ABO809. Participants will have the opportunity to retake the quiz. The quiz should be repeated before any additional screening assessments are obtained.

3.2 ABO809 administration and inpatient monitoring period

ABO809 will be administered at the study site on Day 1. All participants, whether or not they are symptomatic, will be domiciled in a unit with adequate infection control until completion of Day 10 assessments. Participants who experience symptoms will remain domiciled for the duration of the diarrheal illness up to a maximum of Day 21. After Day 10, participants will be released from the study site only after they have had no diarrheal stools for at least 24 hours. Signs, symptoms, stool characteristics and parasitological assessment of oocyst shedding will be monitored daily. Safety assessments will include physical exams, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event and serious adverse event monitoring (see Table 8-1).

3.3 Follow-up period and End of Study

Participants will return for outpatient follow-up visits on Day 14, 17, 21, 24, and 28 for clinical assessments and to provide collected stool samples for analysis. To minimize the risk of long term asymptomatic shedding and recurrence, participants may receive nitazoxanide per the U.S. Prescribing Information (see Section 6.2.3).

If a participant experiences diarrhea after Day 10 (after the participant has been discharged from the study site), the participant may be readmitted, at the discretion of the Investigator, to remain domiciled until the cessation of symptoms or Day 21, whichever is earlier. If diarrhea is not associated with any additional risks to participants, the Investigator can decide that the participant can be managed in an outpatient setting. In this case, the participant is requested to make a reasonable effort to collect all diarrheal stool samples for delivery to the study site. If a participant is still experiencing diarrheal illness at Day 28, the participant's stool will be analyzed for ongoing shedding of oocysts and the participant may be referred to specialty care for further diagnostic work-up and treatment at the discretion of the Investigator.

All participants will return for a follow-up visit on Day 28 to provide collected stool samples. A physical examination and laboratory tests will also be conducted.

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Alternatively, between Day 28 and Day 56, participants may seek medical support from his/her healthcare provider (HCP). Participants may come back to the study site for an unscheduled visit until EOS. The end of study (EOS) visit will occur on Day 56 via phone call. Additional Post-Study Follow-Up phone calls will be conducted after EOS at 6 and 12 months after ABO809 administration. During the phone calls, data will be collected on the development of new onset persistent symptoms that may be related to administration with ABO809, including but not limited to diarrhea, abdominal pain, eye pain and joint pain in all participants (see Section 10.1.1.1).

4 Rationale

4.1 Rationale for study design

Randomization and blinding: All participants will receive ABO809 with a dose escalation strategy (see Section 6.5.1). Therefore the study is not randomized and is not blinded. Participants will be informed about the nature of *Cryptosporidium* infection and potential for asymptomatic infection in healthy adults. The likelihood of potential bias in reporting gastrointestinal symptoms will be mitigated by education of participants prior to enrollment in the study. A residual risk of bias remains in terms of reporting of anticipated symptoms (e.g. abdominal pain, nausea), however, the primary endpoint of oocysts detected in stool samples is objective. Similarly, diarrhea as the expected cardinal symptom of cryptosporidiosis in this study population is at little risk to be confounded by bias. Bias in efficacy endpoints will also be mitigated by having standardized clinical assessments to grade diarrhea and associated symptoms. The use of a central laboratory and validated assays will further decrease bias in safety and efficacy assessments.

ABO809 administration and Inpatient Follow-Up periods: To fully characterize the clinical course of disease, participants will remain domiciled and monitored for safety and study endpoints for 10 days after ABO809 administration. Participants will be discharged from the study site on Day 10 if diarrheal symptoms have been resolved for ≥24 hours. If clinical symptoms still persist on Day 10, the domicile period will be extended until the participant is free of clinical symptoms for ≥24 hours. Based on published data from previous CHIM studies conducted with strains of *C. parvum* and other *Cryptosporidium* species, the median incubation period from time of administration to the onset of diarrhea ranges from 3-11 days, with a median duration of diarrhea ranging from 2.3 to 7 days (see Table 4-1). It is expected that up to 30% or greater of healthy participants may remain asymptomatic after ABO809 administration. If

diarrhea persists at the Day 28 visit, the participant may be referred to specialty care for further diagnostic work-up and treatment at the discretion of the Investigator. A participant can be referred to specialty care earlier at the clinical judgement of the Investigator. This precautionary procedure will be implemented as it is possible that an underlying, previously undetected/unknown condition could contribute to continuing clinical symptoms. In previous CHIM studies, all participants experienced resolution of symptoms and were able to clear *Cryptosporidium* infection.

Outpatient follow-up period: After the domicile period, participants will be followed on an outpatient basis ending on Day 56 following the ABO809 administration. Infection is expected to be self-limiting in healthy adults and resolve by Day 21. Published literature on the intensity of infection and oocyst excretion patterns of *C. parvum* in healthy volunteers suggests that oocyst excretion is limited to the first 14 days in up to 86% participants with diarrhea, and excretion prolonged beyond 28 days is observed in only 5% of participants (Chappell et al 1996). Participants will return for follow-up visits on Day 14, 17, 21, 24 and 28 for physical examination and/or to provide collected stool samples (for measurement of oocyst shedding) (see Table 8-1). Safety Follow-Up Calls will be conducted with participants up to Day 56 to collect adverse events that are considered related to administration with ABO809 (see Section 10.1.1.1). Any participants who experience diarrheal symptoms between Day 28 and Day 56 may provide a stool sample for analysis and may return to the study site for an unscheduled visit to consult with the Investigator.

Treatment with nitazoxanide: Nitazoxanide is a safe and well-tolerated drug approved in the United States to treat diarrhea caused by *Cryptosporidium parvum*. In a 2015 *C. muris* challenge study, two subjects with persistent oocyst shedding were successfully treated with nitazoxanide and the infection was resolved in both subjects, demonstrating the potential of nitazoxanide as a rescue drug (Chappell et al 2015). Following resolution of diarrhea, *C. parvum* infection may be associated with shedding of oocysts with a 21% relapse rate as suggested by the 1993 Milwaukee outbreak (MacKenzie et al 1995). Participants who develop an infection (i.e. oocyst shedding), with or without clinical symptoms will receive a standard 3-day course of nitazoxanide treatment per the U.S. Prescribing Information on Day 21. Given the variability in the onset and duration of oocyst shedding and clinical symptoms in healthy adults, administering nitazoxanide on Day 21 is considered appropriate to enable the full characterization of the study endpoints. Nitazoxanide may be administered earlier, based on clinical findings (see Section 3.3 and Section 6.2.3). Once initiated, nitazoxanide treatment is expected to decrease or eliminate any persistent oocyst shedding to safeguard participants, their household contacts and public health interests. Participants will be informed about reasons of nitazoxanide treatment to improve compliance, which will be recorded in a participant diary. Although nitazoxanide has proven efficacy in reducing oocyst shedding and acute diarrhea in 80-93% of treated participants, there have been no studies looking at the effect of nitazoxanide on the incidence of long-term oocyst shedding or sequelae of cryptosporidiosis. Given this background, Safety Follow-Up Calls will be conducted up to Day 56.

Adaptive study design: The goal is to maximize the incidence of infection. The study cohorts of approximately 10 participants each are designed to enable domiciling of participants in an inpatient unit with adequate infection control, isolation and monitoring. Cohorts are sequential to enable adjustment of the ABO809 dose from one cohort to the next for efficacy and safety reasons. After the Day 14 visit, a Dose Adjustment Data Review will be conducted for the

cohort (see Section 6.5.1) and may result in a dose adjustment for the subsequent cohort. The dose may be adjusted upward to increase the incidence of infection and clinical symptoms or may be reduced due to safety concerns.

End of the Study (EOS): For each participant, the study will end at the Day 56 visit. Additional Post-Study Follow-Up phone calls will be conducted after EOS at 6 and 12 months after ABO809 administration.

4.2 Rationale for dose/regimen and duration of treatment

A total of 10 publications have described CHIM studies conducted with a number of *Cryptosporidium* isolates, including *C. parvum*, *C. hominis*, *C. meleagriditis*, and *C. muris*, with the first study conducted more than two decades ago. These studies aimed to confirm the infectivity of various *Cryptosporidium* species in humans, to identify the human infectious dose, or to explore mechanisms of pathogenesis. Sample size across these published studies is small. The median infectious dose (ID50) among these various *C. parvum* isolates range from 100 to 5,000 oocysts. For the studies conducted with the *C. parvum* Iowa strain in naive patients (seronegative), 100% infectivity (defined by positive detection of oocysts shed in stools) was observed in participants who had received an administration of $\geq 10^3$ oocysts. The highest dose administrated in these studies was 10^6 oocysts. No safety concerns, other than the expected diarrheal illness associated with *Cryptosporidium* infection, were reported for any of the doses or species used for these CHIM studies. No clear relationship between the number of oocysts administered and the presence or severity of clinical syndromes has been described. While the link between the occurrence of diarrhea and size of the inoculum is unclear from published CHIM studies, increasing the size of the inoculum may produce more consistent clinical and parasitological outcomes in a larger proportion of participants.

This CHIM study seeks to safely maximize the incidence of infection and clinical symptoms, and based on the published data, an adaptive study design will be utilized to evaluate oocyst doses of approximately 10^4 up to 10^6 oocysts. The clinical dose is prepared using the most recent available % viability stability data per clinical batch. An administration of 10^4 oocysts has been selected for the first dose-level, and an initial 10 participants will be dosed in cohort 1 at this dose-level. This dose is expected to establish an infection resulting in shedding of *Cryptosporidium* oocysts in the majority of participants, however, the occurrence of clinical symptoms may occur at a lower incidence. If no safety issues are encountered and the desired incidence of infection or clinical diarrheal illness is not achieved (see Section 6.5.1), the anticipated next dose-level is approximately 10^6 oocysts (see Table 6-2). If the clinical symptoms occur at the desired incidence and no safety concerns are observed, additional cohorts will be added to the same dose level. Previously, 10^6 oocysts have been shown to be safe (DuPont et al 1995), however only small numbers of participants (n=7) received doses ≥1000 oocysts. As 10^6 oocysts has been the largest dose administered in previous CHIM studies, no higher dose of ABO809 is considered for this study. Since administration of 10^6 oocysts was not associated with safety concerns, it is considered acceptable to escalate the dose level from 10^4 to 10^6 without intermediate dose levels. This will support reaching the maximally obtainable incidence of infection in a *Cryptosporidium* CHIM with the fewest number of participants enrolled. In the unlikely event of safety concerns associated with any dose, a lower dose may subsequently be used. This dose will be approximately 1 log lower than the previous dose in which safety concerns were noted. Dosing steps between 0.5 and 1 log were used in previous

CHIM studies (see Table 4-1). However, to our knowledge no dose reduction was required at any time in any of these previous CHIM studies since no safety concerns were observed. Since doses of $<10^3$ oocysts did not consistently lead to infection in previous studies (see Table 4-1), a dose lower than approximately 10^3 oocysts is not currently considered for this study.

Details of the dose escalation scheme are provided in Section 6.5.1.

Table 4-1 CHIM studies with *C. parvum*

Species	Dose	N	Infection rate (%)	Diarrhea incidence (%)	Diarrhea incubation (days)	Diarrhea duration (hours)
C. parvum Iowa[1]	30-10^6	29	20-100	0-38	6.5 d[a]	74 h[b]
C. parvum Iowa[2]	5x10^2	19	84	58	8.2 d[b]	60 h[b]
C. parvum Iowa[3]	5x10^2-5x10^4	17	41	59	5 d[a]	155 h[a]
C. parvum UCP[4]	5x10^3-10^4	20	44-100	56-75	6 d[a]	56 h[a]
C. parvum Iowa, UCP, TAMU[5]	10-10^5	60	20-100	52-86	5-11 d[b]	64-95 h[b]
C. parvum Iowa, TAMU[6]	10^2-10^3	15	50-67	33-83	n/a	n/a

[a]expressed as median value

[b]expressed as mean value

[1] DuPont et al 1995, [2]Okhuysen et al 1998a , [3]Chappell et al 1999, [4] Okhuysen et al 1998b, [5] Okhuysen et al 1999, [6] Alcantara et al 2003

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

There is no benefit expected for participants enrolling in this study. All participants will receive thorough medical examinations.

A majority of participants (up to 100% based on prior data) are expected to develop *Cryptosporidium* infection after an oral administration of *C. parvum*. Development of diarrheal illness has been highly variable in previous CHIM studies (see Table 4-1). In one study, 100% of healthy volunteers (n=7) receiving ≥1000 *C. parvum* oocysts, i.e. approximately 10 times above ID50 (median infective dose) developed infection as measured by fecal oocyst shedding; 71% had enteric symptoms, but of these only 29% had diarrheal illness (DuPont et al 1995). The Iowa strain of *C. parvum* used in this study has been suggested to be associated with the shortest duration of diarrhea in comparison to the TAMU and UCP strains (Okhuysen et al 1999).

Cryptosporidiosis typically is a self-limiting infection in immunocompetent adults. The risk to healthy participants is derived from published literature of previous *Cryptosporidium* studies (see Table 4-1), our understanding of the natural history of *Cryptosporidium* infection in healthy adults, and known complications of severe infectious and non-infectious diarrheal illness. Potential risks include:

- **Gastrointestinal cryptosporidiosis**: *Cryptosporidium* can cause asymptomatic infection, mild diarrhea, or severe enteritis with or without biliary tract involvement. Asymptomatic infections have been observed in immunocompetent adults and children with natural infection. This is substantiated in healthy adult human challenge studies, for subjects receiving >1000 oocysts (n=7), 71% had enteric symptoms, but of these only 29% had diarrheal illness (DuPont et al 1995) (see Table 4-1). Diarrhea associated with cryptosporidiosis may be acute or chronic; transient, intermittent or continuous; and scant or voluminous, with up to 25 L/day of watery stool. Patients who develop frequent diarrhea may experience associated malaise, nausea and anorexia, crampy abdominal pain, and low-grade fever. In healthy adults, the illness usually resolves without therapy in 10 to 14 days, although it can persist longer or relapse after initial improvement. Moderate to severe diarrheal illness and associated complications may occur, including but not limited to persistent vomiting, abdominal pain, dehydration, acute renal failure. The risk of severe and/or prolonged disease is increased in patients with cellular and humoral immune deficiencies (e.g. AIDS, organ transplantation, IgA deficiency, hypogammaglobulinemia, and receipt of immunosuppressive therapy); all participants with these conditions will be excluded from the study.

- **Extraintestinal cryptosporidiosis and extraintestinal symptoms of cryptosporidiosis:** A number of other clinical manifestations of cryptosporidiosis have been described in patients with AIDS and prolonged disease. Clinical manifestations can include cholecystitis, cholangitis, hepatitis, and pancreatitis (Chalmers and Davies 2010). Pulmonary involvement has also been described, but it is unclear whether *Cryptosporidium* is a true pathogen or merely colonizes the respiratory tract. Nonspecific respiratory symptoms, including cough, have been reported. Disseminated cryptosporidiosis has not been described. Extraintestinal manifestations, as observed in AIDS patients (Lopez-Velez et al 1995), are expected to be rare in healthy adults. Extraintestinal symptoms of cryptosporidiosis have been reported in immunocompetent patients: it has been suggested that *C. parvum* (used in this study) is less associated with occurrence of non-intestinal sequelae (joint and eye pain, recurrent headache, dizzy spells, fatigue) than *C. hominis* (Hunter et al 2004a) but this is not uniformly reported (Igloi et al 2018). Extraintestinal symptoms of cryptosporidiosis had already occurred more frequently among cases even before infection with *Cryptosporidium* as compared to what was observed in population controls. Hence, people acquiring cryptosporidiosis may be a particular group of the population with a generally increased susceptibility to illness (e.g. people with underlying chronic conditions) (Igloi et al 2018). In this study, participants with chronic/recurring gastrointestinal symptoms will not be enrolled. Extraintestinal manifestations in immunocompetent healthy adults have not been described in the published *Cryptosporidium* human challenge studies (see Table 4-1).
- **Persistent/recurrent illness and non-intestinal sequelae/post-infectious syndromes:** After resolution of the acute infection, longer-term health effects have been described in longitudinal studies of adult outbreak-associated cryptosporidiosis. Self-reported post-infection symptoms up to 12 months included weight loss, abdominal pain, diarrhea, eye pain, joint pain, fatigue, and symptoms consistent with irritable bowel syndrome (Stiff et al 2017). A case-control study found that infection with *C. hominis* (but not *C. parvum*) was associated with joint pain, eye pain, headaches, and fatigue during the two months after infection (Hunter et al 2004b). While there was no difference between *C. parvum* and *C. hominis* infection with regard to post-infectious irritable bowel syndrome, fatigue and abdominal pain were reported more frequently after *C. hominis* infection than after *C. parvum* infection within 1 year after acute infection (Carter et al 2019). Based on this information, participants may continue to have symptoms after resolution of acute infection. In immunocompetent hosts, persistent gastrointestinal and joint symptoms (e.g., painful and inflamed joints involving the knees, ankles, and feet) after natural infection can last for many months after the initial infection (Carter et al 2019, Rehn et al 2015) and may be related in part to the specific species that is causing infection. None of these health concerns have been described in any of the previously conducted *Cryptosporidium* CHIM studies (see Table 4-1). It is not known whether treatment with nitazoxanide may further decrease any potential risk.

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- **Potential adverse events from Nitazoxanide therapy:** Nitazoxanide (Alinia®) will be administered to all participants with *Cryptosporidium* positive stool and/or clinical symptoms on Day 21. Nitazoxanide may be administered earlier to participants with persistent diarrhea on or after Day 10 to resolve diarrheal illness and minimize the risk of shedding or recurrent disease. To avoid unnecessary medication, participants without oocyst shedding at any time after Day 3 and without any diarrhea between Day 1 and Day 21 and without household contacts with diarrhea between Day 10 and Day 21 will not receive nitazoxanide. Nitazoxanide may also be administered as part of "rescue medication" to treat severe diarrheal illness before Day 10 (see Section 6.2.3). The most common adverse reactions in ≥2% of patients were abdominal pain, headache, chromaturia and nausea. In placebo-controlled clinical trials using the recommended dose of nitazoxanide, the rates of occurrence of these events did not differ significantly from those of the placebo. In controlled trials of patients age 12 years and older who received nitazoxanide for the treatment of diarrhea caused by *Giardia lamblia* or *C. parvum*, less than 1% of patients discontinued therapy because of an adverse event (Romark 2017). In the unlikely event that symptoms persist, the participant will, at the discretion of the Investigator, obtain additional diagnostic work-up and subsequent therapy (potentially including a second course of nitazoxanide) as appropriate (see Section 6.2.3).

The risks to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close monitoring. Refer to the Investigator's Brochure.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation will be collected during the Screening/Baseline, Inpatient Follow-Up and Outpatient Follow-Up portions of the study (up to 8 weeks total). Additional samples may be required for safety monitoring. The timing and intended use of blood samples is outlined in the Assessment Schedule (see Table 8-1). Instructions for sample collection, processing, storage and shipment information are available in the Laboratory Manual. See Section 8.5.1.2 on the potential use of residual blood samples.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

The study population will be comprised of adult male and female healthy participants. Up to approximately 60 participants may be enrolled in the study.

The Investigator must ensure that all participants being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the Investigator, in order that the study population will be representative of all eligible participants.

Participant selection is to be established by checking through all eligibility criteria at Screening and Baseline. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a participant from enrollment into the study. See Section 9.1.1.1 for information on replacement participants.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent from the participant must be obtained prior to participation in the study.
2. At Screening, participants will be educated on facts about *Cryptosporidium* disease, safety measures and transmission risks. Participants must then score 100% on a quiz assessing their understanding of *Cryptosporidium* infection and transmission. Participants will have the opportunity to retake the quiz. The quiz should be repeated before any additional Screening assessments are obtained.
3. Male and female participants must be between 18 to 50 years of age and in good health as determined by medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at Screening and Baseline.
4. At Screening and Baseline, vital signs will be assessed in the sitting position, and must be within the following ranges:
   - oral body temperature between 35.0-37.0 ^{o}C
   - systolic blood pressure between 90-139 mmHg
   - diastolic blood pressure between 59-89 mmHg
   - pulse rate between 50-90 bpm
5. Participants must weigh at least 50 kg, and have a body mass index (BMI) within the range of 18-30 kg/m^2.

6. Ability to communicate well with the Investigator, and to understand and comply with the requirements of the study including restrictions provided in Section 6.2.4.
7. Participant must be in compliance with current local COVID-19 testing policies.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

No additional exclusions may be applied by the Investigator, in order to ensure that the study population will be representative of all eligible participants.

1. History of *Cryptosporidium* infection.
2. Current (based on screening laboratory tests) or history of infectious diarrhea associated with international travel in the last 12 months or *C. difficile* infection within 6 months prior to Screening.

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6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and dispensing and taking study treatment will be outlined in the Pharmacy Manual. If vomiting occurs within 30 minutes of administration of ABO809 a second administration of ABO809, at the same dose may be given.

6.1.1 Investigational and control drugs

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	**Pharmaceutical Dosage Form**	**Route of Administration**	**Supply Type**
ABO809, $3x10^6$ CE/3 mL	Concentrate for oral suspension	Oral use	Open label bulk supply; glass vials

CE, *C. parvum* oocysts
No control drug will be used in this study.

6.1.2 Additional study treatments

Participants may receive nitazoxanide (see Section 6.2.3).

Table 6-2 Additional Study Treatment

Drug (Name and Strength)	**Pharmaceutical Dosage Form**	**Route of Administration**	**Supply Type**
Nitazoxanide 500 mg	Tablet	Oral use	Bottle

Nitazoxanide to be provided by clinical site

6.1.3 Supply of study treatment

Refer to Pharmacy Manual.

6.2 Other treatment(s)

Participants may receive nitazoxanide and/or other treatments as detailed below.

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant is enrolled into the study must be recorded on the appropriate Case Report Forms. Fluid replacement (e.g. as needed with diarrheal symptoms) will be recorded as a concomitant medication.

Each concomitant medication must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before administering a new medication.

6.2.2 Prohibited medication

Except for protocol allowed concomitant medication or any medication which may be required to treat adverse events, no medication other than study treatment will be allowed from the date the participant signs the inform consent until EOS.

Participants should not receive any antiperistaltic, antidiarrheal agents or stool softeners from Screening through Day 28. These agents include, but are not limited to, bismuth subsalicylate, atropine and diphenoxylate, loperamide, octreotide, opium tincture, cholestyramine, colestipol, colace, or lactulose. Participants should not consume yogurt, kefir or probiotics (e.g. *Saccharomyces boulardii)* up to Day 21 or initiation of nitazoxanide, whichever comes first. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant is enrolled into the study must be recorded on the appropriate Case Report Forms.

In addition, other than those administered per protocol, participants should not receive any antibacterial or anti-parasitic therapy with possible activity against *Cryptosporidium* up to Day 28 (see Section 6.2.3).

Warfarin or drugs that prolong the QTc interval are not permitted between Screening and Day 28 unless deemed necessary by the Investigator (participants on warfarin or drugs that prolong the QTc interval are not permitted to enter the study (see Section 5.2).

Vaccinations are not permitted between Day -14 and Day 28 but are permitted outside this window (including COVID-19 vaccinations).

6.2.3 Rescue medication

To minimize the risk of severe clinical illness, long-term asymptomatic shedding and recurrence of *Cryptosporidium* infection, nitazoxanide may be administered at 500 mg by mouth every 12 hours with food for 3 days as per the U.S. Prescribing Information, under the clinical conditions outlined below. Nitazoxanide is the standard of care for the treatment of cryptosporidiosis. In double-blind, controlled trials in adults and adolescents with diarrhea and with or without enteric symptoms caused by *C. parvum*, nitazoxanide administered at 500 mg BID for 3 days resulted in a 96% clinical response rate 4 to 7 days following the end of treatment. In this study, clinical response was defined as "no symptoms, no watery stools and no more than 2 soft stools within the past 24 hours" or "no symptoms and no unformed stools within the past 48 hours" (Romark 2017).

All participants who receive ABO809 and develop an infection (i.e. oocyst shedding after Day 3), will receive nitazoxanide on Day 21 or as soon as EIA analysis CCI of Day 17 sample becomes available whether or not they develop clinical symptoms. There are conditions under which participants may receive nitazoxanide earlier: (i) participants with diarrhea persisting until Day 10 will start nitazoxanide on Day 10, (ii) participants with severe diarrheal illness (≥ Grade 3 as per Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007)) may receive

nitazoxanide unless deemed contraindicated by the Investigator irrespective of timing. Whenever nitazoxanide treatment is administered to participants experiencing clinical symptoms, participants may be domiciled at the discretion of the Investigator until free of clinical symptoms for ≥24 hours.

A second course of nitazoxanide and/or other antiparasitic drug(s) (e.g. paromomycin alone or in combination with azithromycin) may be considered for participants with severe diarrhea or treatment failure after nitazoxanide monotherapy at the discretion of the Investigator. The duration of treatment will depend upon the participant's response to therapy. Although controlled, large-scale trials are lacking, the use of combination therapy is supported by findings from small case series (Smith et al 1998). Paromomycin (500 mg three times daily for one week) is generally used as an alternative agent if nitazoxanide cannot be used. All antimicrobial therapy for cryptosporidiosis administered before Day 28 will be recorded in eCRF as a concomitant medication.

Participants will not receive nitazoxanide if:

- they did not shed oocysts at any time after Day 3 and
- they did not have diarrhea between Day 1 and Day 21 and
- there was no diagnosis of cryptosporidiosis in any of the participant's household contacts between Day 11 and Day 21

In participants with severe diarrheal illness, oral and/or intravenous hydration, and replacement of electrolytes as needed, is expected as part of the standard of care management of adverse events (dehydration and severe diarrhea). Fluid replacement therapy will be recorded as a concomitant medication in the eCRF.

6.2.4 Restriction for study participants

Participants should be informed and reminded of the restrictions outlined in this section.

6.2.4.1 Dietary restrictions and smoking

- No alcohol from Day-2 until after the Day 28 visit.
- No cannabis use from Screening until after the Day 28 visit.
- No cigarettes/use of nicotine products from Screening until the Day 28 visit.
- Only thoroughly cooked meat, fish and seafood will be allowed from Day-4 until after the Day 28 visit (all meat must be "well done" so that no red is evident).
- Participants should not consume yogurt, kefir or probiotics (e.g. *Saccharomyces boulardii)* up to Day 21 or initiation of nitazoxanide, whichever comes first.

Meals will be provided when all study procedures scheduled for that time have been completed.

6.2.4.2 Other restrictions

- No strenuous physical exercise (e.g. weight training, aerobics, football) from Day 1 until discharged
- Participants must abstain from using public pools and waterparks from Day 1 until after the Day 28 visit. Refraining from using private swimming pools is also recommended.

- Employment as a healthcare worker with direct patient care, in a daycare center (for children or the elderly), or direct food handler (individuals who work directly with food in commercial establishments) is prohibited between Screening and Day 28.
- Sharing a home with a pregnant woman or anyone <7 years old or >65 years old, infirmed, or immunocompromised is prohibited between Screening and Day 28.
- Sexual practices that may increase the risk of fecal-oral transmission of *Cryptosporidium* should be avoided or appropriate safety measures used from Day 1 until after the Day 28 visit. Participants will be informed about CDC recommendations to practice safer sex in case of cryptosporidiosis.
  (Parasites-Cryptosporidium-Prevention & Control-General Public 2019):
  - Wait to have sex (vaginal, anal, and oral) for 2 weeks after you no longer have diarrhea.
  - Reduce your contact with stool during sex by:
    - Washing your hands, genitals, and anus with soap and water before and after sexual activity
    - Using barrier methods during sex. Barrier methods include condoms, dental dams, and cut-open condoms. Sex includes oral (mouth-to-penis, mouth-to-vagina, mouth-to-anus), anal (penis-to-anus), and vaginal (penis-to-vagina) sex
    - Using latex gloves during anal fingering or fisting
    - Using condoms the right way, every time you have anal and vaginal sex, which will also help prevent other sexually transmitted infections
    - Washing your hands with soap and water immediately after touching a used condom or other barrier method
    - Washing sex toys with soap and water after each use, and washing hands after touching used sex toys

Participants will receive educational material explaining all applicable restrictions and recommendations to avoid spread of *Cryptosporidium* oocysts.

6.2.4.2.1 Additional Recommendations

Handwashing Procedures

Alcohol-based sanitizers are not effective against *Cryptosporidium*. Use of good hygiene practices, especially washing hands with soap and water is essential, in particular at the following key times (When and How to Wash Your Hands 2020):

- Before, during, and after preparing food
- Before and after eating food
- Before and after caring for someone who is sick with vomiting or diarrhea
- Before and after treating a cut or wound
- After using the toilet
- After changing diapers or cleaning up a child who has used the toilet
- After blowing your nose, coughing, or sneezing

- After touching an animal, animal feed, or animal waste
- After handling pet food or pet treats
- After touching garbage
- There can also be other times when it is important to wash hands

House-cleaning Procedures

Participants will be informed that *Cryptosporidium* is not sensitive to chlorine or bleach disinfectants and no disinfectant is completely effective against *Cryptosporidium.* The chance of spreading the infection can be lowered by recommended cleaning procedures, which will be provided to the participants:

(Parasites – Cryptosporidium – General Information for the Public)

- Wash linens, clothing, dishwasher- or dryer-safe soft toys, etc. soiled with feces or vomit as soon as possible
- Flush excess vomit or feces on clothes or objects down the toilet
- Wash linens, clothing, etc. soiled with feces or vomit as soon as possible
- Use laundry detergent and wash in hot water (113°F or hotter for at least 20 minutes or 122°F or hotter for at least 5 minutes)
- Machine dry on the highest heat setting

For other household objects and surfaces:

- Remove all visible feces
- Clean with soap and water
- Let dry completely for at least 4 hours (if possible, expose to direct sunlight during the 4 hours)

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each individual may participate only once in this study and will be identified by a Participant Number (Participant No.) that will be assigned when the participant is enrolled for screening and will be retained for the participant throughout his/her participation in the study. A new Participant No. will be assigned at every subsequent enrollment if the participant fails screening and is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

The informed consent procedures need to be re-started if the Investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

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6.4 Treatment blinding

Treatment will be open to participants, investigator staff, person performing the assessments and the Novartis clinical trial team (CTT).

6.5 Dose escalation and dose modification

Prior to any dose adjustment, a review of efficacy and safety/tolerability data in the dose cohort will be performed, in order to decide about dose escalation.

6.5.1 Dose escalation guidelines

Data to be reviewed for dose escalation

After each cohort, and prior to any dose adjustment for the subsequent cohort, a review of all available safety data will be performed to determine if it is safe to dose additional participants in subsequent cohorts.

The data to be reviewed to inform dose-adjustment include the incidence of clinical symptoms and the incidence of infection up to Day 10, as well as all available safety information including safety information obtained up to Day 14, AEs, safety laboratory assessments (hematology, chemistry, urinalysis), ECGs, vital signs, physical examination) for that cohort.

Criteria for dose escalation

The Sponsor and site Investigator will perform a joint Dose Adjustment Data Review after all participants in a cohort have completed the Day 14 visit, with the expectation that 10 participants will provide evaluable data. Evaluable data is defined as data received from any participant who provided at least one stool sample for parasitological assessment and/or in whom we have a clinical evaluation of potential diarrheal illness via CHIM diary or AE reporting with at least two diarrheal bowel events within 24 hours after ≥72 hours post administration of ABO809. For definitions of infection and diarrheal illness, see Section 3. If there are no safety concerns that will prevent continuation of a given dose level or dose escalation, the dose escalation decision will be guided by the following criteria. If at the data review the criteria below are achieved, a subsequent cohort may be dosed at the current dose level:

- There are approximately 80%-90% of participants showing infection
- There are approximately 60%-70% of participants showing diarrheal illness

Otherwise, a dose escalation decision may be made. The decision will take into consideration the totality of data available at the time of decision making.

In the case of safety concerns associated with any ABO809 dose, the next cohort may be dosed with an inoculum approximately one order of magnitude smaller than the preceding one. For example, if safety concerns are noted in the cohort receiving an inoculum of approximately 10^6

oocysts, the next cohort of 10 participants may be dosed with an inoculum of approximately 10^5 oocysts (see Section 6.5.1.2).

Safety Review Team

Participating functions (tasks can be delegated to appropriately qualified deputies) in all safety reviews include:

- Sponsor
  - medical lead
  - operational lead
  - research lead (optional)
  - statistician (optional)
  - biomarker expert (optional)
- Study site
  - Investigator
  - operational lead

Additional functions can be added on an ad-hoc basis.

For timing of safety data reviews see Section 4.4 (Purpose and timing interim analyses), Section 6.5.1 (Dose escalation), and Section 9.1.4 (Study stopping rules).

6.5.1.1 Starting dose

The starting dose to be administered to the first cohort of 10 participants will be a single dose of approximately 10^4 oocysts administered as oral suspension to be taken with approximately one glass of water (approximately 200 mL).

6.5.1.2 Provisional dose levels

Table 6-3 describes the starting dose and the maximum dose level that may be evaluated during this trial; additional doses between $1x10^3$ and $1x10^6$ may be considered.

Table 6-3 Provisional dose levels

Dose level	Oocyst dose (approximate viable oocyst count)
Starting dose	$1x10^4$
Maximum dose	$1x10^6$

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Each participant will be supervised while receiving their single dose of ABO809, and will be domiciled for a minimum of 10 days to support compliance with study requirements.

6.6.2 Recommended treatment of adverse events

Based on the expected symptomatology following *Cryptosporidium* administration, treatment to stabilize electrolyte and water homeostasis may need to be initiated. This may include parenteral fluid administration and, in case of persistent clinical symptoms, the administration of medications (see Section 6.2.3).

Any interventions to treat adverse events (AEs) must be recorded on the appropriate eCRF.

6.7 Preparation and dispensation

The study site will be supplied with ABO809 in packaging as described in the Investigational and control drugs section (see Section 6.1.1). A unique medication number will be printed on the study medication label. ABO809 should be prepared/diluted as per the instructions for use provided in the Pharmacy Manual.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Corporate Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of the country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a Drug Accountability Log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused nitazoxanide and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed Drug Accountability Log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

Table 6-4 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
ABO809, $3x10^6$ CE/3m L	Approximate oocyst count $1x10^3$ - $1x10^6$	A single dose on Day 1

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
Nitazoxanide (Rescue medication)	500 mg	Every 12 hours with food for 3 days

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved Informed Consent.

Informed Consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining Informed Consent must be documented in the participant source documents.

Novartis will review the study site proposed Informed Consent form to ensure it complies with the ICHE6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any further changes to the proposed consent form suggested by the Investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about ABO809 and nitazoxanide can be found in Section 4.5, the Investigator's Brochure (IB) and the USPI for nitazoxanide. This information will be included in the participant Informed Consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of ABO809 that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification (IN) or an aggregate safety finding. New information might require an update to the Informed Consent and must be discussed with the participant.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic, or natural disaster, that may challenge the ability to obtain a standard written Informed Consent due to limits that prevent an on-site visit, Investigator may conduct the Informed Consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining Informed Consent, etc.).

The following Informed Consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment

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Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Participants may be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the Assessment Schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from the study treatment are to return for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule.

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The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic, or natural disaster, that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/home nursing staff to the participant home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Participants may be asked to check-in to the study site prior to Day 1 to undergo additional COVID-19 precaution procedures.

Table 8-1 Assessment Schedule

Period	Screening		Treatment	In-Patient Follow-Up									Outpatient Follow-Up								
Visit Name	Screening	Baseline	Treatment	Inpatient Follow-Up									Outpatient Follow-Up Visits					Safety Follow-Up Call			End of Study Call
Visit Number	1	2	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	199
Days	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	14	17	21	24	28	35	42	49	56
Informed consent	X																				
Understanding of Cryptosporidium Infection & Transmission Quiz	S																				
Medical history/current medical conditions	X																				
Physical Examination	S	S										S					S				

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Period	**Screening**		**Treatment**	**In-Patient Follow-Up**									**Outpatient Follow-Up**								
Visit Name	**Screening**	**Baseline**	**Treatment**	**Inpatient Follow-Up**									**Outpatient Follow-Up Visits**					**Safety Follow-Up Call**			**End of Study Call**
Visit Number	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**113**	**114**	**115**	**116**	**117**	**118**	**199**
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**14**	**17**	**21**	**24**	**28**	**35**	**42**	**49**	**56**
Inclusion / Exclusion criteria	S	S																			
Demography	X																				
Alcohol Test, Drug Screen, and Cotinine Test	S	S																			
SARS-CoV2 Screen	X	X																			
Hepatitis screen	S																				
HIV screen	S																				
Thyroid stimulating hormone	X																				
T4 (Free)	X																				
Pregnancy[2]	X	X															X				
Body Height	X																				
Body Weight[11]	X	X	X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Vital Signs[11]	X	X	X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Electrocardiogram (ECG)[11]	X	X	X[3]									X					X				
Hematology[11]	X		X[3]									X					X				
Clinical Chemistry[11]	X		X[3]									X					X				
Urinalysis[11]	X	X	X[3]									X					X				
ABO809 administration			X																		

Period	Screening		Treatment	In-Patient Follow-Up									Outpatient Follow-Up								
Visit Name	Screening	Baseline	Treatment	Inpatient Follow-Up									Outpatient Follow-Up Visits					Safety Follow-Up Call			End of Study Call
Visit Number	1	2	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	199
Days	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	14	17	21	24	28	35	42	49	56
Participants domiciled[13]		X																			
Stool Collection [12]	X	X	X	X	X	X	X	X	X	X	X	X	X[4]	X[4]	X[4]	X[4]	X[4]				
Occult Blood	X	X		X		X		X		X		X									
Cryptosporidium Antigen by EIA[10, 12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
IgA	X																				
Evaluation of Clinical Signs and Symptoms[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
CHIM Diary		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	X[14]				
Standard of Care Drug Administration (Nitazoxanide)[8]															X						

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Period	**Screening**		**Treatment**	**In-Patient Follow-Up**									**Outpatient Follow-Up**								
Visit Name	**Screening**	**Baseline**	**Treatment**	**Inpatient Follow-Up**									**Outpatient Follow-Up Visits**					**Safety Follow-Up Call**			**End of Study Call**
Visit Number	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**113**	**114**	**115**	**116**	**117**	**118**	**199**
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**14**	**17**	**21**	**24**	**28**	**35**	**42**	**49**	**56**
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Safety Follow-Up Call for Study Participants																		S	S	S	S
Study completion information																					X

Period	**Post-Study Follow-Up**	
Visit Name	**Post-Study Follow-Up Call**	
Days	**6 Month Phone Contact**	**12 Month Phone Contact**
Informed consent		

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Understanding of Cryptosporidium Infection & Transmission Quiz		

Period	**Post-Study Follow-Up**	
Visit Name	**Post-Study Follow-Up Call**	
Days	**6 Month Phone Contact**	**12 Month Phone Contact**
Medical history/current medical conditions		
Physical Examination		
Inclusion / Exclusion criteria		
Demography		
Alcohol Test, Drug Screen, and Cotinine Test		
SARS-CoV2 Screen		
Hepatitis screen		
HIV screen		
Thyroid stimulating hormone		
T4 (Free)		
Pregnancy[2]		
Body Height		
Body Weight[11]		
Vital Signs[11]		
Electrocardiogram (ECG)[11]		
Hematology[11]		
Clinical Chemistry[11]		
Urinalysis[11]		
ABO809 administration		
Participants domiciled[13]		
Stool Collection[12]		

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Occult Blood		
Cryptosporidium Antigen by EIA[10, 12]		

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Period	**Post-Study Follow-Up**	
Visit Name	**Post-Study Follow-Up Call**	
Days	**6 Month Phone Contact**	**12 Month Phone Contact**

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IgA		

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Evaluation of Clinical Signs and Symptoms[6]		
CHIM Diary		
Standard of Care Drug Administration (Nitazoxanide)[8]		
Concomitant medications		
Adverse Events	S[15]	S[15]

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Safety Follow-Up Call for Study Participants	S	S
Study completion information		

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[2] Serum pregnancy tests at Screening and Day 28. Urine pregnancy test at Baseline.
[3] Before ABO809 administration.
[4] Participants should make every attempt to bring self-collected stool specimen to the clinic for each Outpatient Follow-Up visit. In the 24 hours prior to each Outpatient Follow-Up visit, all stools should be collected.
[5] During screening, the first diarrheal stool, and the first diarrheal stool with relapse after clinical clearance will be tested for enteral pathogenic micro-organisms.
[6] Includes number and frequency of diarrheal episodes, stool weight, volume, and grading (see Section 8.3.2, Section 8.4.1, and Appendix 1). Additionally, includes evaluation of nausea, vomiting, abdominal pain or discomfort, abdominal tenderness, abdominal rebound, abdominal distension, fecal urgency, diarrhea, flatulence, tenesmus, poor appetite, dehydration, fever, and electrolyte imbalance

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[8] Nitazoxanide to be administered per Prescribing Information (i.e. 500 mg every 12 hours for 3 days). Nitazoxanide administration will be captured on the standard concomitant medication page, and no specific CRF is required.

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Period	**Post-Study Follow-Up**	
Visit Name	**Post-Study Follow-Up Call**	
Days	**6 Month Phone Contact**	**12 Month Phone Contact**

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[11] Additional tests can be done at the discretion of the Investigator e.g., in the case of dehydration.

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[13] All participants, whether or not they are symptomatic, will be domiciled in a unit until completion of Day 10 assessments. Participants who experience symptoms will remain domiciled for the duration of the diarrheal illness up to a maximum of Day 21. If a participant experiences diarrhea after Day 10 (after the participant has been discharged from the study site), the participant may be readmitted, at the discretion of the Investigator, to remain domiciled until the cessation of symptoms or Day 21, whichever is earlier.

[14] CHIM diary eCRF page will capture only if the diary was fully complete or not. No data from the diary will be recorded on this diary eCRF page. AEs will be captured on the standard AE eCRF, and nitazoxanide administration will be captured on the standard concomitant medication eCRF page.

[15] Adverse events of special interest (AESI) defined in Section 10.1.1.1 will be recorded at the 6 and 12 month Post-Study Follow-up calls as source data and reported to Novartis Safety if the Investigator considers there is a reasonable possibility that ABO809 caused the event, unless otherwise specified by local law/regulations.

8.1 Screening

It is permissible to re-screen a participant once if s/he fails the initial Screening (see Section 5.1). Participants need to re-consented (see Section 7) for re-screening and a new participant number must be assigned (see Section 6.3).

In the case where a safety laboratory assessment at Screening and/or Baseline is outside of the range specified in the eligibility criteria (see Section 5.2), the assessment may be repeated once. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

8.1.1 Eligibility screening

Results of below screening measurements will be available as source data at the study site and will not be recorded within the eCRF unless specified below.

8.1.1.1 Hepatitis screen, HIV screen

All participants will be screened for Hepatitis B surface antigen (HBsAg) and, if standard local practice, Hepatitis B core antigen (HBcAg). Screening for Hepatitis C will be based in HCV antibodies and if positive, HCV RNA levels should be determined.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmed by a second technique available at the laboratory site or a central lab e.g. Western blot. Appropriate counseling will be made available by the Investigator in the event of a positive confirmatory test. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

8.1.1.2 Alcohol test, Drug screen, Urine cotinine

Participants will be tested for evidence of alcohol and substances of abuse (e.g. alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids including tetrahydrocannabinol (THC), cocaine and opiates). Each participant will be tested for urine cotinine levels.

8.1.1.3 Understanding of Cryptosporidium Infection & Transmission Quiz

Participants will be educated on facts about *Cryptosporidium* disease, safety measures and transmission risks. They must then score 100% on a quiz assessing their understanding of *Cryptosporidium* infection and transmission. Participants will have the opportunity to retake the quiz.

8.1.1.4 SARS CoV-2 Screen

As applicable by local guidelines and regulations, participants will undergo testing of SARS CoV-2 infection to be allowed to participate in the study. COVID-19 prevention policies will be followed. SARS CoV-2 screen results will be entered into the database.

8.1.2 Information to be collected on screening failures

Participants who sign an Informed Consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable

Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.3).

Participants who sign an Informed Consent and are considered eligible but fail to receive a dose of ABO809 for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form.

8.2 Participant demographics/other baseline characteristics

Participant demographics including full date (only if required and permitted) or year of birth or age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, the diversity of the study population will be assessed as required by Health Authorities.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See Section 6.2.1 (Concomitant Therapy) for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

8.3.1 Cryptosporidium Antigen by EIA

To assess the incidence of *Cryptosporidium* infection, fresh stool samples will be collected at Screening and during the study as detailed in the Assessment Schedule (see Table 8-1). While participants are domiciled, all stools will be collected for grading and quantity record, however, up to 3 stool samples per day, each separated by approximately 4 hour intervals, will be analyzed by EIA CCI at a CLIA laboratory for parasitological assessment of oocyst shedding. If the participant passes less than 3 stools on any given day during domiciling (1 or 2) then these stool samples will be used for parasitological assessment.

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8.3.2 Evaluation of Clinical Signs and Symptoms

To assess the incidence and characteristics of cryptosporidiosis, the signs and symptoms associated with cryptosporidiosis will be monitored as described in the Assessment Schedule (Table 8-1).

Onset, progression, improvement and resolution of signs and symptoms associated with *Cryptosporidium* infection will be recorded in the eCRF at Baseline and approximately

every 8 hours during the Inpatient Follow-Up period, at Outpatient Follow-Up visits/Safety Follow-Up Calls and at any unscheduled visits. Symptoms of cryptosporidiosis will be AEs; these and any SAEs will be recorded as such (see Section 10).

Diarrhea is defined as at least one stool sample grading 3-5 on the Stool Grading System (see Section 16.1) in one day. Grades 3-5 stools are defined as thick liquid diarrhea taking the shape of the container, opaque watery, rice water or clear watery stools. Diarrhea will be further characterized by measuring the form of the stool, the total weight of stool, the number and frequency of diarrheal episodes and the time to resolution of diarrheal illness.

Diarrhea data will be collected as follows: onset, progression, total stool output (weight in grams) and severity of diarrhea (Grading will be assessed using the U.S. Food and Drug Administration's (FDA) "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007)"; the worst grade each day will be recorded).

Data on other gastrointestinal symptoms associated with *Cryptosporidium* infection will be recorded in the eCRF as follows: presence (yes/no), onset, severity (mild, moderate, severe), therapeutic intervention (yes/no; if yes what) and progression (ongoing, resolved). These gastrointestinal symptoms include:

- abdominal pain or discomfort
- abdominal tenderness
- abdominal rebound
- abdominal distension
- fecal urgency
- nausea/vomiting
- flatulence
- tenesmus
- poor appetite
- presence of blood
- fever

Since nausea/vomiting, diarrhea, headache, fatigue, and myalgia are listed in the US FDA "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007)" these symptoms should be graded according to provided definitions in the guidance document (compare Section 10.1.1).

Other symptoms the Investigator considers potentially related to ABO809 administration will also be recorded in the eCRF as free text.

A participant will be considered as showing clinical diarrheal illness if diarrhea is observed on at least two days during the observation period beginning after the ABO809 administration (Day 1) and ending on Day 28.

Resolution of diarrheal illness from *Cryptosporidium* infection requires ≥2 consecutive days with no diarrheal stools (stool sample grades 1 or 2).

8.3.2.1 CHIM Diary

Participants will provide a health and stool update daily from Day 1 to Day 28 in a Participant CHIM Diary. Any clinical symptoms, and/or diarrheal episodes associated with *Cryptosporidium* infection should be recorded. The Diary will be submitted to the site at Day 28.

8.3.3 Appropriateness of efficacy assessments

Presence of *Cryptosporidium* oocysts in the stool following oral administration is well established as an indicator of *Cryptosporidium* infection (DuPont et al 1995). Analysis of stool by EIA CCI is considered an appropriate method to detect the presence of fecal *Cryptosporidium* oocysts (see Section 8.3.1).

Systematic measurement and assessment of cryptosporidiosis-associated signs and symptoms (see Section 8.3.2) and AEs (see Section 10) are considered appropriate to assure participant safety and qualify/quantify the illness expected to be elicited by ABO809 administration.

8.4 Safety

Safety assessments are specified in the Assessment Schedule (see Table 8-1 which details when each assessment is to be performed.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 2 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-2 Assessments and Specifications

Assessment	Specification
Physical Examination	A complete physical examination at screening will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. At other visits, a shorter physical exam may be performed to include the examination of general appearance. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the eCRF. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the eCRF.

Assessment	Specification
Vital Signs	Vital signs will include the collection of body temperature (recorded in °C), blood pressure (BP) and pulse measurements. After the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated arm device, e.g. OMRON with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. If vital signs are out-of-range at screening and/or baseline (see Inclusion Criteria Section 5.1 of the protocol for details), two additional readings can be obtained, so that up to three consecutive assessments are made, with the participant seated quietly for approximately five minutes preceding each repeat assessment. The last reading must be within the ranges provided in the eligibility criteria in order for the participant to qualify. In case of repeated vital assessments, the eCRF should contain all repeat measurements
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Body mass index (BMI) will be calculated using the following formula: · BMI = Body weight (kg) / [Height (m)]2 The Screening Visit height measurement will be used for BMI calculations throughout the study.

Additional laboratory assessments, vital signs assessments, physical exams, ECGs and other safety measures can be conducted any time when indicated in the opinion of the investigator (e.g. in case of diarrheal illness with substantial loss of fluid volume, orthostatic dysregulation, fever).

For details on AE collection and reporting, refer to Section 10.1.

8.4.1 Laboratory evaluations

Clinically significant abnormalities must be recorded either as medical history/current medical conditions or adverse events as appropriate.

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance shall be made by the Investigator in consultation with the Sponsor. The decision shall be based upon the nature and degree of the observed abnormality. The assessment may be repeated at Screening.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

A local laboratory will be used for analysis of all safety specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the central laboratory manual.

Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

Special clinical laboratory evaluations

Refer to Section 8.3.2

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Table 8-3 Laboratory Assessments

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count. Coagulation testing including prothrombin time (PT) (also reported as INR) and activated partial thromboplastin time (aPTT)

Test Category	Test Name
Chemistry	Sodium, potassium, creatinine, BUN or urea, uric acid, chloride, albumin, calcium, magnesium, alkaline phosphatase, total bilirubin (direct and indirect), bicarbonate/HCO3, LDH, GGT, AST, ALT, amylase, lipase, CK, glucose, total cholesterol, triglycerides and total protein
Urinalysis	Dipstick measurements for bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen will be performed. If dipstick measurement results are positive (abnormal),then microscopy must be assessed with results loaded into the database. Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Thyroid	T4 [free], TSH
Screening Tests	Hepatitis (HBV-DNA, HBsAg, HBsAb, HBcAb, HCV RNA-PCR), HIV screen, alcohol test, drug screen, urine cotinine
Pregnancy Test	Serum / Urine pregnancy test

8.4.2 Electrocardiogram (ECG)

All ECGs will be measured after a 10 minute rest in the supine position. The following parameters will be reported: PR interval, QRS duration, heart rate, RR interval, QT interval and QTcF interval.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions: $QTcF = QT/(RR/1s)^{1/3}$

As applicable, QTcF and QTcB may be calculated at the site. Unless auto-calculated by the ECG machine, the Investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility and continuation in the study.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated, e.g. in the case of dehydration.

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical condition or adverse event as appropriate.

8.4.3 Pregnancy

All pre-menopausal women who are not surgically sterile will be tested for pregnancy at Screening, Baseline and the Day 28 visit. Additional pregnancy testing might be performed if requested by local requirements.

At Screening and on Day 28, a serum pregnancy test will be performed. A urine pregnancy test will be performed at Baseline. During the study duration, urinary pregnancy tests are sufficient. In case the pregnancy urine test is positive, the result needs to be confirmed with serum test. Pregnancy testing information will be captured in the database.

8.4.4 Appropriateness of safety measurements

The safety assessments selected cover all standard assessments for studies in healthy participants. In addition, the assessments address the potential health impact of a *C. parvum* oocyst administration, which is expected to results in diarrhea and other mainly gastrointestinal symptoms as well as potential changes in water and electrolyte balance.

Commercially Confidential Information

8.5 Additional assessments

Additional assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

9 Study discontinuation and completion

9.1 Discontinuation and completion

This is a single dose study, therefore discontinuation of study treatment is not applicable.

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation from study treatment is when the participant permanently stops receiving ABO809 and further protocol-required assessments or follow-up for any reason.

If a participant agrees to a final evaluation at the time of the participant's discontinuation, the evaluation should be performed as detailed in the assessment schedule (see Section 8).

Stopping the study for an individual participant can be initiated by either the participant or the Investigator. There is no discontinuation of ABO809 administration since this is a single dose study. The Investigator must discontinue the study for a given participant if he/she believes that continuation would negatively impact the participant's safety.

The study must be discontinued for an individual participant under the following circumstances:

- Participant decision
- The Investigator believes that continuation would negatively impact the safety of the participant or the risk/benefit ratio of study participation
- Any other protocol deviation that results in a significant risk to the participant’s safety prior to dosing
- Any confirmed COVID -19 case that warrants discontinuation of the study for the participant in the judgment of the Investigator or Sponsor to protect the safety of the participant, other study participants or study site staff

Participants who discontinue the study or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2). Where possible, they should return for the assessments as indicated in the Assessment Schedule (see Table 8-1).

Participants who discontinue from the study after ABO809 administration will be treated with nitazoxanide as described in Section 4.1.

If participants fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the participant as specified in the Lost to follow-up section (see Section 9.1.3).

After a participant discontinues the study, the following data should be collected at clinic visits or via telephone/email contact if possible:

- New / concomitant treatments
- AEs / SAEs

Participants meeting study discontinuation and stopping criteria will continue to be monitored for safety if possible and will be included in the safety analyses.

9.1.1.1 Replacement policy

Participants will not be replaced on this study. Should fewer than 10 participants be evaluable in a given cohort, the number of participants may be increased in subsequent cohorts. A total of up to 6 sequential cohorts may be enrolled (see Section 4 and Section 6.5).

9.1.2 Withdrawal of informed consent

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

The Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

ABO809 administration must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.1.3 Lost to follow-up

If the participant cannot or is unwilling to attend any Outpatient Follow-Up visit(s), the site staff should maintain regular telephone contact with the participant if possible. This telephone contact should preferably be done according to the Schedule of Assessments.

For participants whose status is unclear because they fail to appear for Outpatient Follow-Up visits and/or 6 and 12 month Safety Follow-Up Calls without stating an intention to discontinue or withdraw, the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Study stopping rules

Dosing of ABO809 will be done approximately simultaneously by cohort. The temporal spacing between one cohort and the next is anticipated to be approximately 21 days. Dosing of additional participants may be stopped due to safety concerns. Participants who have already been dosed with ABO809 at the time safety concerns become apparent will continue in the study until the Day 56 visit is completed (see Section 3 and Section 4).

Dosing in this study may be placed on hold if safety concerns are observed, and a safety review will be conducted within approximately 48 hours. No further dosing will take place until this safety review is completed.

Criteria leading to a decision to not dose additional participants are:

- One or more ABO809 related-SAEs, such as signs and symptoms of extra-intestinal cryptosporidiosis or complications.
- At least 2 of the participants in the same cohort experience a similar AE which is assessed as severe in intensity, and is potentially related to study treatment (illness consistent with gastrointestinal cryptosporidiosis which is expected and desired in the context of this study is not in scope for this criterion)
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold

Should a decision be made to not dose additional participants, already dosed participants will continue to be monitored for safety and included in the safety analysis (Safety Follow-Up Calls will be conducted).

Dosing of the next cohort / additional participants may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed (also see Section 8.4).

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time. Potential reasons for early termination may include but are not limited to:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Discontinuation of ABO809 clinical supply

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from dosing of ABO809 (see Section 9.1.4). The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Sponsor, depending on the local regulations, will be responsible for informing IRBs/IECs of the early termination of the study.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their EOS visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

Each participant will be required to complete the study in its entirety.

All participants who received ABO809 should have a safety follow-up call conducted approximately 60 days after administration of ABO809. All AEs reported during this time period must be reported as described in Section 10.1.3.

Post-study Follow-Up calls scheduled after the EOS visit will be conducted at 6 and 12 months after the Day 1 visit to collect adverse event of special interest (AESI) information.

Documentation of attempts to contact the participant should be recorded in the source documentation.

10 Safety monitoring and reporting

As part of a CHIM study, AEs associated with *Cryptosporidium* infection are expected.

AEs and SAEs will be monitored, treated and appropriately recorded by the Investigator from Day 1 until EOS (Day 56). AESI information will be collected at the 6 month and 12 month Post-Study Follow-Up Phone Calls.

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease in a participant after providing written informed consent for participation in the study. An AE is temporally associated with the use of a medical treatment or procedure and may or may not be considered related to the medical treatment or procedure.

The Investigator has the responsibility for managing the safety of individual participants and identifying adverse events. Expected symptoms following *Cryptosporidium* infection are described in Section 8.3.2 and in the Investigator's Brochure (IB).

All clinical signs and symptoms associated with *Cryptosporidium* infection will be characterized as AEs and entered in the eCRF. The AE should be described using the diagnosis "Gastrointestinal Cryptosporidiosis," rather than listing individual underlying signs and symptoms.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

Recording and Grading of AEs

Adverse events may be detected through physical examination findings, laboratory test findings, or other assessments made by site personnel or when they are volunteered by the participant during or between visits. Information on adverse events must be obtained by non-directive questioning of the participant.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than only individual underlying signs and symptoms.

All AEs must be recorded and accompanied by the following information (as far as possible):

1. The AE severity grade:

Grading will be assessed using the U.S. Food and Drug Administration's (FDA) "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007)". For AE reporting based on laboratory values, local laboratory normal ranges may be used at the discretion of the Investigator, and if so, must be used consistently throughout the study. These may differ from the normal ranges given in the FDA grading scale. In case of such discrepancies, the Investigator will take into consideration the FDA

recommendations as to the magnitude of deviations from normal provided in the FDA grading scale.

For AEs that are not contained in the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007)", the following categorization will be used:

- Mild: usually transient in nature and generally not interfering with normal activities
- Moderate: sufficiently discomforting to interfere with normal activities
- Severe: prevents normal activities

2. The AE relationship (causality) to the study treatment will be assessed for all AEs recorded during treatment and follow-up by the investigator. The criteria for assessing the AE relationship to the study treatment are listed below:

    a. Related – There is reasonable possibility that the study treatment caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study treatment and the AE.

    b. Not related – There is no reasonable possibility that the administration of the study treatment caused the event.

3. The AE duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported

4. Whether the AE constitutes an SAE (see Section 10.1.2 for the SAE definition)

5. Its outcome (i.e. recovery status or whether it was fatal)

AEs Follow-up

All adverse events must be treated appropriately. Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Once an adverse event is detected, assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome. AEs must be followed, in person or by phone call as appropriate, until resolution or until judged to be permanent (i.e. unresolved at the EOS).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease.

10.1.1.1 Adverse events of special interest

All participants may report adverse events associated with *Cryptosporidium* infection as detailed in Section 4.5 Risks and benefits. The Investigator will report AESI and follow-up accordingly; these include:

- **Gastroenteritis in the absence of *Cryptosporidium* infection**: In the event of gastroenteritis in the absence of *Cryptosporidium* infection, the event will be considered an AESI. The Investigator will investigate other potential causes of diarrhea, including infectious diarrhea and manage participant's care according to local standards.
- **Extraintestinal cryptosporidiosis:** *Cryptosporidium* infection involving the biliary tract, lungs, liver, pancreas, or other organs will be considered AESI (also see Section 4.5 Risks and benefits).
- **Persistent or recurrent cryptosporidiosis:** Persistent clinical symptoms after administration of standard of care, or after initial resolution of *Cryptosporidium* oocysts in the stool and/or diarrheal symptoms, will be considered an AESI.
- **Persistent *Cryptosporidium* shedding:** Persistent detection of *Cryptosporidium* oocysts in stools after treatment with nitazoxanide will be considered an AESI. Participants with persistent shedding may be treated with combination therapy as detailed in Section 6.2.3.
- **Dehydration:** Moderate or severe dehydration, as defined below will be considered an AESI.
  - **Mild:** dry mucous membranes; diminished skin turgor; increased oral fluids are indicated
  - **Moderate:** IV fluids are indicated
  - **Severe:** hospitalization is indicated or it is considered to have life-threatening consequences; or an urgent intervention is indicated
- **Non-intestinal sequelae:** Development of new onset non-intestinal symptoms, including eye pain or joint pain, will be considered AESI.

If any AESIs are experienced after EOS (i.e. Post-Study Safety Follow-up calls at 6 and 12 months) in which the Investigator considers there is a reasonable possibility that ABO809 caused the event, the event will be recorded and reported following the same procedure as SAEs as described in Section 10.1.3. These AESIs will be captured in the Novartis safety database, included in an addendum to the CSR and reported to the competent authorities and relevant ethics committees as per national regulatory requirements in participating countries.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of or worsening of any pre-existing] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- Fatal
- Life-threatening

A life-threatening SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death

if it were more severe (please refer to the ICH E2D (2004) Clinical Safety Data Management: Definitions and Standards for expedited reporting).

- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Social reasons and respite care in the absence of any deterioration in the participant's general condition
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - Is medically significant, i.e. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH E2D (2004) Clinical Safety Data Management: Definitions and Standards for expedited r eporting).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of ABO809 are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until EOS (Day 56) must be reported to Novartis Safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to the study site. Information about all AEs is collected and recorded on the Serious Adverse Event Report Form: all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode

within 24 hours of the Investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to ABO809, a CMO & PS Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with ABO809 that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees as per national regulatory requirements in participating countries.

If any SAEs are experienced after EOS (i.e. Post-Study Safety Follow-up calls at 6 and 12 months) in which the Investigator considers there is a reasonable possibility thatABO809 caused the event, the event should be recorded, reported, and captured in the Novartis safety database. All such SAEs will be included in an addendum to the CSR and reported to the competent authorities and relevant ethics committees as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

Pregnancies

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, are excluded from study unless they are using highly effective methods of contraception while in the study (see Section 5.2). Therefore, pregnancies are not expected during the study.

However, if a female trial participant becomes pregnant, ABO809 must not be administered (if detected before dosing), and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review, and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. If the pregnancy is detected between Day 1 and EOS the pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should also be collected for the female partners of any males who received ABO809 in this study if the calculated day of conception is between Day 1 and EOS. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

The newborn conceived between Day1 and EOS will be followed up for a minimum of 1 year after delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Nitazoxanide errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Novartis Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the nitazoxanide errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional nitazoxanide error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 10.1.1 and Section 10.1.2.

10.2 Additional Safety Monitoring

Not applicable

11 Data Collection and Database management

11.1 Data collection

The Investigator or designated staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements; the Investigator and site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator or designated staff.

The Investigator/designee is responsible for assuring that the data (recorded on eCRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

Certain data may be captured via other source documentation (such as safety laboratory data report) and then transcribed, uploaded or transferred into the system. This, and any additional data treated in this manner, will be source data verified by the Novartis study monitor per the monitoring plan and the location of source data (i.e., source, paper or a local electronic system) will be documented prior to study start in the Data Quality Plan. The system has the ability to illustrate when a document has been entered from another source. When using an electronic source record as the original point of data capture, there is no additional data entry step for the site for data collected directly into the application; rather, the electronic source record directly populates the study database. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Sponsor. Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational site staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. The Investigator or designated site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis or delegated CRO representative will review the protocol and data capture requirements (i.e. eSource or eCRFs) with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the site's data. The Novartis field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored,

dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of the site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The Investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The Investigator must give the Novartis monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary and secondary objectives. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed,

12 Data analysis and statistical methods

The statistical analysis of this study will be performed by Novartis or a designated CRO. Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation. Procedures for data analysis will be further specified in the Statistical Analysis Plan (SAP). A Clinical Study Report (CSR) will be prepared following the Day 56 visit.

12.1 Analysis sets

For all analysis sets, participants will be analyzed according to the dose of ABO809 (*C. parvum* oocysts, also referred to as "treatment").

The safety analysis set will include all participants that received ABO809.

The PD analysis set includes all participants with available safety, parasitological and clinical data and with no protocol deviations with relevant impact on PD data.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data will be listed and summarized descriptively by treatment for all participants. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. All demographic data and data on other baseline characteristics (e.g., alcohol, HIV and hepatitis screening etc.) will be listed by treatment and participant in detail. Relevant medical history, current medical conditions, results of laboratory screens, and any other relevant information will be listed by treatment and participant.

12.3 Treatments

Dose administration will be listed by treatment arm, date and time.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary endpoint is *Cryptosporidium* infection (detection of oocysts in fecal samples by EIA CCI at ≥72 hours post-administration or sooner if associated with symptoms suggestive of diarrheal illness) up to Day 10 (inclusive). The 10 day observation window may be extended as described in Section 4.1.

12.4.1 Statistical model, hypothesis, and method of analysis

The number and proportion (in percentage) of participants with *Cryptosporidium* infection will be summarized. The lower limit of the 1-sided 80% exact confidence interval of the proportions will also be reported.

12.4.2 Supplementary analysis

Not applicable.

12.5 Analysis of secondary endpoints/estimands

The secondary endpoints include the presence of clinical symptoms (diarrheal and associated symptoms) by Day 10 and Day 28 as described in Section 8.3.2, *Cryptosporidium* infection up to Day 28, time to infection and symptom on-set, time to resolution of infection and diarrheal illness, and characteristics of clinical signs and symptoms associated with diarrheal illness, as well as safety and tolerability endpoints.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The number and proportion (in percentage) of participants with clinical symptoms (by Day 10 (inclusive) and Day 28) and with *Cryptosporidium* infection up to Day 28 will be summarized by treatment. The lower limit of the 1-sided 80% exact confidence interval of the proportions will be reported by treatment. The clinical symptoms are defined as diarrheal and associated gastrointestinal symptoms, evaluated from symptom onset up to Day 10. The observation window for clinical symptoms may be extended as described in Section 4.1.

Frequency and percentage will be presented for categorical data such as grading of stool consistency and number of diarrhea episodes. Mean, standard deviation, median, minimum, and maximum will be presented for continuous data such as stool weight. On-set, duration, time to resolution of infection and diarrheal illness as well as severity of other clinical signs and symptoms associated with diarrheal illness (including but not limited to abdominal pain, abdominal cramping, nausea, vomiting, fever, electrolyte imbalance, dehydration) will be analyzed as appropriate. Details will be documented in the Statistical Analysis Plan.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include data from Day 1 until the EOS with the exception of Baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on-treatment and post treatment deaths will be provided.

Adverse events

The number (and percentage) of participants with adverse events will be summarized in the following ways:

- by Primary system organ class and preferred term
- by Primary system organ class and preferred term and maximum severity

Separate summaries will be provided for ABO809 related AEs, SAEs, AESIs and deaths.

A participant with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG findings

For ECG parameters, summary statistics for baseline value, actual assessment values, and change from baseline values will be presented by time of measurement. All ECG data will be listed; notably abnormal values will be flagged, and the overall interpretation of abnormality will be presented.

Clinical laboratory evaluations

Clinical laboratory data will include chemistry, hematology and urinalysis results up to EOS.

All laboratory values will be converted into International System of Units (SI) units. If grades are not defined by the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007), results will be graded by the low/normal/high classifications based on laboratory normal ranges. Continuous laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) by time point.

12.6 Analysis of exploratory endpoints

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12.7 Interim analyses

Commercially Confidential Information

Commercially Confidential Information

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Approximately 10 participants in each cohort will be enrolled to receive ABO809. The sample size is driven by practical reasons. Assuming the true incidence of infection is 90%, there is at least 80% chance to claim that the incidence is at least 78% with a sample size of 30 participants, and 74% with a sample size of 20 participants, and 81% with a sample size of 60 participants. The calculation is based on the 1-sided 80% exact confidence interval.

12.8.2 Secondary endpoint(s)

Assuming the true incidence of clinical symptoms is 70%, there is at least 80% chance to claim that the incidence is at least 53% with a sample size of 30 participants, and 48% with a sample size of 20 participants, and 58% with a sample size of 60 participants. The calculation is based on the 1-sided 80% exact confidence interval.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is

requested by a regulatory authority, the Investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

This study only involves healthy volunteers and as such Novartis will register the protocol as required to databases specified by local regulations (e.g. clinicaltrials.gov during CTA filing). After study completion and finalization of the study report, results of this trial may be submitted for publication (e.g. peer-reviewed journal) or registered to databases where required by local regulations.

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials provided at the site initiation visit.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of Investigator sites, vendors, and Novartis systems are performed by auditors independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving ABO809 under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

Alcantara CS, Yang CH, Steiner TS, et al (2003) Interleukin-8, tumor necrosis factor-alpha, and lactoferrin in immunocompetent hosts with experimental and Brazilian children with acquired cryptosporidiosis. Am J Trop Med Hyg p. 325-8.

Carter BL, Stiff RE, Elwin K, et al (2019) Health sequelae of human cryptosporidiosis-a 12-month prospective follow-up study. Eur J Clin Microbiol Infect Dis p. 1709-1717.

Chalmers R, Davies A (2010) Minireview: clinical cryptosporidiosis. Exp Parasitol Jan 2010; 124(1):138-46

Chappell CL, Okhuysen PC, Langer-Curry R (2015) Cryptosporidium muris: infectivity and illness in healthy adult volunteers. Am J Trop Med Hyg 92:50-55

Chappell CL, Okhuysen PC, Langer-Curry R, et al (2006) Cryptosporidium hominis: experimental challenge of healthy adults. Am J Trop Med Hyg 75:851-857.

Chappell CL, Okhuysen PC, Sterling CR, et al (1996) Cryptosporidium parvum: intensity of infection and oocyst excretion patterns in healthy volunteers. J Infect Dis. 1996 Jan;173(1):232-6.

Chappell CL, Okhuysen PC, Sterling CR, et al (1999) Infectivity of Cryptosporidium parvum in healthy adults with pre-existing anti-C. parvum serum immunoglobulin G. Am J Trop Med Hyg p. 157-64.

Checkley W, Epstein LD, Gilman RH, et al (1998) Effects of Cryptosporidium parvum infection in Peruvian children: growth faltering and subsequent catch-up growth. Am J Epidemiol p. 497-506.

Checkley W, Gilman RH, Epstein LD, et al (1997) Asymptomatic and symptomatic cryptosporidiosis: their acute effect on weight gain in Peruvian children. Am J Epidemiol p. 156-63.

Checkley W, White AC, Jaganath D, et al (2015) A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium. Lancet Infect Dis p. 85-94.

Chen XM, Keithly JS, Paya CV, et al (2002) Cryptosporidiosis. N Engl J Med; 346(22): 1723-1731.

Colussi O, Rouen A, Seksik P, et al (2010) Acute cryptosporidiosis as a cause of sudden recurrence of digestive symptoms in patients with Crohn's disease. J Crohns Colitis p. 669-70.

Cron RQ, Sherry DD (1995) Reiter's syndrome associated with cryptosporidial gastroenteritis. J Rheumatol p. 1962-3.

Darton TC, Blohmke CJ, Moorthy VS, et al (2015) Design, recruitment, and microbiological considerations in human challenge studies. Lancet Infect Dis p. 840-51.

DuPont HL, Chappell CL, Sterling CR, et al (1995) The infectivity of Cryptosporidium parvum in healthy volunteers. N Engl J Med p. 855-9.

Guerrant RL, DeBoer MD, Moore SR, et al (2013) The impoverished gut--a triple burden of diarrhoea, stunting and chronic disease. Nat Rev Gastroenterol Hepatol p. 220-9.

Hunter PR, Hughes S, Woodhouse S, et al (2004a) Health sequelae of human cryptosporidiosis in immunocompetent patients. Clin Infect Dis p. 504-10.

Hunter PR, Hughes S, Woodhouse S, et al (2004b) Sporadic cryptosporidiosis case-control study with genotyping. Emerg Infect Dis p. 1241-9.

ICH E2D (2004) Clinical Safety Data Management: Definitions and Standards for expedited reporting. Accessed from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002807.pdf Accessed on: 02Dec2016.

Igloi Z, Mughini-Gras L, Lochlainn L (2018) Long-term sequelae of sporadic cryptosporidiosis: a follow-up study. Eur J Clin Microbiol Infect Dis. 2018;37(7):1377-1384

Insulander M, Silverlas C, Lebbad M (2013) Molecular epidemiology and clinical manifestations of human cryptosporidiosis in Sweden.2013;141:1009-1020

Kotloff KL, Nataro JP, Blackwelder WC, et al (2013) Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet p. 209-22.

Levine MM, Kaper JB, Herrington D, et al (1988) Safety, immunogenicity, and efficacy of recombinant live oral cholera vaccines, CVD 103 and CVD 103-HgR. Lancet p. 467-70.

Lopez-Velez R, Tarazona R, Garcia Camacho A (1995) Intestinal and extraintestinal cryptosporidiosis in AIDS patients. Eur J Clin Microbiol Infect Dis. 1995; 14(8):677-81

Mac Kenzie WR, Hoxie NJ, Proctor ME, et al (1994) A massive outbreak in Milwaukee of cryptosporidium infection transmitted through the public water supply. N Engl J Med; 331(3):161-167

MacKenzie WR, Kazmierczak JJ, Davis JP (1995) An outbreak of cryptosporidiosis associated with a resort swimming pool. Epidemiol Infect p. 545-53.

Okhuysen PC, Chappell CL, Sterling CR, et al (1998a) Susceptibility and serologic response of healthy adults to reinfection with Cryptosporidium parvum. Infect Immun 66:441-443.

Okhuysen PC, Chappell CL, Crabb J, et al (1998b). Prophylactic effect of bovine anti-Cryptosporidium hyperimmune colostrum immunoglobulin in healthy volunteers challenged with Cryptosporidium parvum. Clin Infect Dis 26:1324-1329.

Okhuysen PC, Chappell CL, Crabb JH, et al (1999) Virulence of three distinct Cryptosporidium parvum isolates for healthy adults. J Infect Dis p. 1275-81.

Ozgül A, Tanyüksel M, Yazicioglu K, et al (1999) Sacroiliitis associated with Cryptosporidium parvum in an HLA-B27-negative patient. Rheumatology (Oxford) p. 288-9.

Painter JE, Hlavsa MC, Collier SA, et al (2015) Cryptosporidiosis surveillance -- United States, 2011-2012. MMWR Suppl p. 1-14.

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents (2018). Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America (Internet) Available from: (Accessed 25 February 2019).

Parasites – Cryptosporidium – General Information for the Public (Internet) Available from: (Accessed 06 October 2021)

Parasites-Cryptosporidium-Prevention & Control-General Public (2019) (Internet) Available from: (Accessed 15-Feb-2021)

Platts-Mills JA, Babji S, Bodhidatta L, et al (2015) Pathogen-specific burdens of community diarrhoea in developing countries: a multisite birth cohort study (MAL-ED). Lancet Glob Health p. e564-75.

Pollard AJ, Savulescu J, Oxford J, et al (2012) Human microbial challenge: the ultimate animal model. Lancet Infect Dis p. 903-5.

Putignani L, Menichella D (2010) Global distribution, public health and clinical impact of the protozoan pathogen cryptosporidium. Interdiscip Perspect Infect Dis. 2010:1-39

Rehn M, Wallensten A, Widerström M, et al (2015) Post-infection symptoms following two large waterborne outbreaks of Cryptosporidium hominis in Northern Sweden, 2010-2011. BMC Public Health p. 529.

Romark L (2017). ALINIA® (nitazoxanide) prescribing information (Internet) Available from: (Accessed 25 February 2019)

Sack DA, Tacket CO, Cohen MB, et al (1998) Validation of a volunteer model of cholera with frozen bacteria as the challenge. Infect Immun p. 1968-72.

Smith NH, Cron S, Valdez LM, et al (1998) Combination drug therapy for cryptosporidiosis in AIDS. J Infect Dis p. 900-3.

Stiff RE, Davies AP, Mason BW (2017) Long-term health effects after resolution of acute Cryptosporidium parvum infection: a 1-year follow-up of outbreak associated cases. Journal of Medical Microbiology 66:1607-1611

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007). Guidance for Industry. U.S. Food and Drug Administration (Internet) Available from: (Accessed 09 July 2021).

Tribble DR, Baqar S, Carmolli MP, et al (2009) Campylobacter jejuni strain CG8421: a refined model for the study of Campylobacteriosis and evaluation of Campylobacter vaccines in human subjects. Clin Infect Dis p. 1512-9.

When and How to Wash Your Hands (2020) (Internet) Available from: (Accessed 15 February 2021)

16 Appendices

16.1 Appendix 1: Stool Grading System

All collected stool samples will be graded according to the system detailed below. Stools will be graded according to this Stool Grading System by the Investigator. Grades 1 and 2 are considered normal stool and Grades 3-5 are considered diarrheal stool.

Table 16-1 Stool Grading System

Clinical Stool Classification	Stool Grade	Stool Description
Normal stool	1	Formed stool which does not take the shape of the container
Normal stool	2	Soft stool which does not easily take the shape of the container
Diarrheal stool	3	Thick liquid stool which does take the shape of the container
Diarrheal stool	4	Opaque watery stool
Diarrheal stool	5	Rice water stool, clear watery stool

Levine et al 1988, Sack et al 1998, Tribble et al 2009