TITLE PAGE

Protocol Title:

A 3-part, Phase 1a/1b, first-in-human, randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, and pharmacokinetics of single and multiple ascending doses of oral CDX-7108 in healthy adult subjects and to evaluate proof-of-concept via pharmacodynamics of a single dose of oral CDX-7108 in subjects with exocrine pancreatic insufficiency.

Protocol Number: 2102CLI

Version: 1.0 (Original Protocol)

Product: CDX-7108

Short Title: Phase 1a/1b single and multiple ascending dose study of oral CDX-7108 in healthy adult subjects and a single dose proof-of-concept study of oral CDX-7108 in subjects with exocrine pancreatic insufficiency.

Study Phase: Phase 1a/1b

Sponsor Name: Nestlé Health Science, Société des Produits Nestlé.

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Date of Protocol: 28 May 2021

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

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Medical Monitor name and contact information can be found in Appendix 1.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body mass index
CF	Cystic fibrosis
COVID-19	Coronavirus disease 2019
C_{max}	Maximum serum concentration
CP	Chronic pancreatitis
CRO	Contract research organization
CS	Clinically significant
$C_{ss,max}$	Maximum steady state serum concentration
CSR	Clinical Study Report
CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiograms
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOS	End-of-study
EPI	Exocrine pancreatic insufficiency
ET	Early termination
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GLP	Good laboratory practice
HDEC	Health and Disability Ethics Committee
HREC	Human Research Ethics Committee
HRT	Hormone replacement therapy
IB	Investigator’s Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
INR	International normalized ratio

Abbreviation	Definition
IP	Investigational product
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MTG	Mixed triglyceride
NCS	Not clinically significant
NOAEL	No-observed-adverse-effect level
PD	Pharmacodynamics
PERT	Pancreatic enzyme replacement therapy
PI	Principal Investigator
PK	Pharmacokinetics
POC	Proof-of-concept
PPI	Proton-pump inhibitors
PT	Preferred term
QID	Four times a day
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAD	Single ascending dose
SAE	Serious adverse event
SARS-CoV-2SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SOC	System organ class
SOP	Standard operating procedures
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
TEAEs	Treatment-emergent adverse events
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopoeia
WOCBP	Woman of childbearing potential

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A 3-part, Phase 1a/1b, first-in-human, randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, and pharmacokinetics of single and multiple ascending doses of oral CDX-7108 in healthy adult subjects and to evaluate proof-of-concept via pharmacodynamics of a single dose of oral CDX-7108 in subjects with exocrine pancreatic insufficiency.

Short Title:

Phase 1a/1b single and multiple ascending dose study of oral CDX-7108 in healthy adult subjects and a single dose proof-of-concept study of oral CDX-7108 in subjects with exocrine pancreatic insufficiency.

Rationale:

No clinical studies have yet been performed with CDX-7108 and its effects in humans are unknown. This is the first-in-human (FIH) study of CDX-7108, which aims to assess the safety, tolerability, pharmacokinetics (PK) of escalating single and multiple oral doses of CDX-7108 in healthy adult subjects and to evaluate the pharmacodynamics of a single dose of oral CDX-7108 in a proof-of-concept (POC) study in subjects with exocrine pancreatic insufficiency (EPI).

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety, and tolerability of single and multiple ascending oral doses of CDX-7108 in healthy subjects, as well as of a single therapeutic dose in subjects with EPI.	• The safety parameters to be assessed include AEs/SAEs and changes in clinical laboratory tests, vital signs, 12-lead ECG, and physical examination from baseline
Secondary	
• To characterize the PK profile of single and multiple ascending oral doses of CDX-7108 when administered with food in healthy subjects.	• Serum concentration-time profile of CDX-7108 • The serum PK parameters include: o Part A (SAD): AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and $t_{1/2}$ o Part B (MAD): $AUC_{0-\tau}$, AUC_{0-t}, $C_{ss,max}$, Day 1 to Day 6 C_{τ} (predose), T_{max}, and $t_{1/2}$
• To exclude changes in overall serum lipase activity after administration of single and multiple ascending oral CDX-7108 when administered with food in healthy subjects.	• Serum lipase activity
• To explore the preliminary PD of a single therapeutic dose of CDX-7108 in subjects with EPI as assessed by measurement of lipid absorption (Pancreo-Lip® breath test).	• The PD parameters of CDX-7108 include: o Percentage $^{13}CO_2$ excretion rate over baseline (% dose/h) o 150_{min} percentage $^{13}CO_2$ excretion rate (% dose/h) o Percentage $^{13}CO_2$ cumulative excretion at 240 minutes (% dose)
Tertiary	
• To evaluate immunogenicity of single and multiple ascending oral doses of CDX-7108 in healthy subjects, as well as of a single therapeutic dose in subjects with EPI.	• Development of anti-CDX-7108 antibodies

Abbreviations: AE = adverse event; AUC_{0-inf} = area under the concentration-time curve from time zero to infinity;

AUC_{0-t} = area under the concentration-time curve from time zero to the last sampling time; $AUC_{0-\tau}$ = area under the concentration-time curve over the dosing interval (τ) at steady state; C_{max} = maximum serum concentration; $C_{ss,max}$ = maximum concentration at steady sate; C_{τ} = predose concentration over the dosing interval (τ); $^{13}CO_2$ = carbon dioxide; ECG = electrocardiogram; EPI = exocrine pancreatic insufficiency; MAD = multiple ascending dose; PD = pharmacodynamic; PK = pharmacokinetic; SAD = single ascending dose; SAE = serious adverse event; T_{max} = time to maximum serum concentration; $t_{1/2}$ = terminal elimination half-life.

Overall Design:

This is an integrated 3-part study to investigate the safety, tolerability, PK, and PD of CDX-7108. The Parts A and B are randomized, double-blind, placebo-controlled dose escalation parts to investigate the safety, tolerability, immunogenicity, and PK of CDX-7108 after single and multiple oral dose administration in healthy adult subjects. Part C is a randomized, double-blind, placebo-controlled, single-dose, 2-way crossover part to assess POC of CDX-7108 in terms of PD as well as its safety, tolerability, and immunogenicity in subjects with EPI. The study will commence with Part A (single ascending dose [SAD] study) and will progress to Part B (multiple ascending dose [MAD] study), and Part C (POC study) as described below. A study schema is provided in Figure 1.

Part A (SAD study):

In this study part, single-dose administration of CDX-7108 at the following anticipated dose levels. 10 000, 50 000, 150 000, 250 000, and 500 000 lipase units will be evaluated in 5 sequential cohorts of 6 subjects each. The study duration per subject will be approximately 7 weeks (including Screening).

Subjects will undertake a Screening visit between Day −28 and Day −1 to determine their eligibility for the study. Subjects who meet the eligibility criteria will be admitted to the study site on the day prior to dosing (Day −1), during which their continued eligibility will be assessed up to Day 1 prior to dosing. Subjects will be randomized on Day 1 and will receive a single oral dose of CDX-7108 or matched placebo in 30 mL of oral dosing solution including flavored syrup together with a standard breakfast, which should be consumed at the study site within 20 minutes of the start of the meal.

Within each cohort, safety, tolerability, PK, and serum lipase activity assessments will be performed at predefined time points as specified in the Schedule of Assessments. Subjects will remain at the study site for observation up to the morning of Day 2 after all 24-hour postdose assessments have been performed and samples collected, and will be discharged thereafter. Subjects will return to the study site on an outpatient basis on Day 8 for a Follow-up visit and then on Day 22 for the End-of-study (EOS) visit. The EOS visit will also be the early termination (ET) visit if required.

As this is a FIH study, a sentinel dosing strategy will be employed for each dose cohort in the SAD study. Each cohort will include 2 sentinel subjects (1 CDX-7108: 1 placebo) who will be dosed first and monitored by the Investigator for a minimum of 24 hours prior to dosing the rest of the cohort. Once the dose is deemed to be safe and well tolerated in the sentinel subjects by the Investigator, in consultation with the independent Medical Monitor and Sponsor as needed, the remaining 4 subjects in the cohort (3 CDX-7108, 1 placebo) will be administered the investigational product (IP) without the requirement of a formal Safety Review Committee (SRC) decision. The decision to dose the rest of the cohort will be documented.

Part B (MAD study)

MAD study will evaluate multiple dose administration of CDX-7108 at an appropriate low (50 000 lipase units), mid (150 000 lipase units), and high dose (250 000 lipase units) 4 times a day (QID) for 6 consecutive days in 3 sequential cohorts of 6 subjects each. Part B (MAD study) will commence only after the completion and SRC review of the data from the third single dose cohort (150 000 lipase units) in Part A (SAD study). Dose level decisions for Part B (MAD study) will be guided by the emerging safety, tolerability, and PK data from Part A (SAD study) as well as from Part B (MAD study).

Subjects will undertake a Screening visit between Day −28 and Day −1 to determine their eligibility for the study. Subjects who meet the eligibility criteria will be admitted to the study site on the day prior to

dosing (Day −1), during which their continued eligibility will be assessed up to Day 1 prior to dosing. Eligible subjects will be randomized on Day 1 and will receive oral dose of CDX-7108 or placebo QID in 30 mL of oral dosing solution including flavored syrup from Day 1 to Day 6 together with a meal (breakfast, lunch, afternoon snack, and dinner), which should be consumed within 20 minutes of the start of the meal. Meals will be provided at regular intervals of 4 hours.

Within each cohort, safety, tolerability, PK, and serum lipase activity assessments will be performed at predefined time points as specified in the Schedule of Assessments. Subjects will remain at the study site for observation up to the afternoon of Day 7 (18 hours post-last-dose) and will be discharged after all assessments have been performed and samples collected. Subjects will return to the study site on an outpatient basis on Day 15 for a Follow-up visit and then on Day 29 for an EOS visit. The EOS visit will also be the ET visit if required.

Part C (POC study)

This part of the study is designed as 2-way crossover design with a 7-day washout period. A total of 10 subjects with severe EPI from partial/total pancreatectomy or chronic pancreatitis will be enrolled. It is anticipated that Part C (POC study) will commence after completion of the third single-dose cohort (150 000 lipase units) from Part A (SAD study) and following SRC review of the data from this cohort; this dose level is expected to be therapeutically active in subjects with severe EPI. However, a different dose level could be selected depending on emerging safety, tolerability, and PK data from Part A (SAD study).

Subjects will undertake a Screening visit between Day −35 and Day −1 to determine their eligibility for the study. Subjects who meet the eligibility criteria will be admitted to the study site on the day prior to dosing (Day −1), during which their continued eligibility will be assessed up to Day 1 prior to dosing. Subjects will be randomized in a 1:1 ratio to one of the 2 treatment sequences: CDX-7108 →placebo or placebo→CDX-7108 on Day 1. Following an overnight fast on Day 1 and Day 8, subjects will not receive their usual pancreatic enzyme replacement therapy (PERT) but instead will receive a single oral dose of CDX-7108 or matched placebo in 30 mL of oral dosing solution including flavored syrup together with a standardized breakfast containing ^{13}C mixed triglyceride (Pancreo-Lip breath test substrate), which should be consumed within 10 minutes of the start of the meal. Then they will remain fasted for at least 4 hours postdose, following which food accompanied by their usual PERT will be permitted.

Pharmacodynamic assessments using a Pancreo-Lip breath test, as well as safety and tolerability assessments will be performed at predefined time points as specified in the Schedule of Assessments. Following dosing on Day 1, subjects will remain at the study site for observation and collection of postdose samples and will be discharged the same day. Subjects will then return to the study site on Day 7 and will receive CDX-7108 or matched placebo on Day 8; following dosing, subjects will remain at study site for postdose samples and will be discharged thereafter. Subjects will visit the study site on an outpatient basis on Day 15 for a Follow-up visit and then on Day 29 for an EOS visit. The EOS visit will also be the ET visit if required.

Number of Investigators and Study sites:

This study will be conducted multiple sites in New Zealand and Australia.

Number of Subjects:

Approximately 58 subjects will be enrolled in this study. Approximately 48 adult healthy male and female subjects will be enrolled in at least 5 cohorts in Part A (SAD study) and at least 3 cohorts in Part B (MAD study). In Parts A and B, each cohort will include 6 subjects (4 receiving CDX-7108 and 2 receiving placebo) with at least 2 male and 2 female subjects. Additional subjects (6 per cohort) may be enrolled if it is deemed appropriate or necessary by the SRC to repeat a dose level in a new cohort of

subjects or to study an interim dose level. Approximately 10 subjects with severe EPI will be enrolled in Part C (POC study) of the study.

Treatment Groups and Duration:

- In Part A (SAD study), 5 cohorts are planned and subjects will receive a single dose of CDX-7108 or placebo on Day 1. The study duration per subject will be approximately 7 weeks (including Screening).
- In Part B (MAD study) 3 cohorts are planned and subjects will receive CDX-7108 or placebo QID for 6 days. The study duration per subject will be approximately 8 weeks (including Screening).
- In Part C (POC study), subjects will receive a single dose of CDX-7108 and placebo separated by a 7-day washout period as per their treatment sequence allocation. The study duration per subject will be approximately 9 weeks (including Screening).

Criteria for Pausing/Stopping Dose Escalation and Study:

If any of the following scenarios occur, dose escalation or the study may be paused/stopped. If any of the below criteria are met in Part A (SAD study), then progression to Part B (MAD study) and Part C (POC study) will occur only at dose levels deemed to be safe and well tolerated in Part A.

- ≥1 subject experiences SAEs considered to be related to the IP.
- ≥2 subjects experience severe AEs of the same character considered to be related to the IP.
- ≥1 subject meets 1 of the following liver chemistry stopping criteria in alignment with the United States Food and Drug Administration premarketing clinical liver safety guidance:
    - Alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) (or ALT ≥3 × ULN and international normalized ratio [INR] >1.5), termed “Hy’s Law”. This event must be reported as an SAE.
    - ALT ≥5 × ULN
    - ALT ≥3 × ULN, if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity (such as fatigue, nausea, vomiting, pain, or tenderness in the right upper quadrant, fever, rash, or eosinophilia)
- ≥2 subjects who receive the IP have a QTc prolongation defined as QT interval corrected for heart rate using Fridericia’s formula (QTcF) >500 msec, or an increase of QTcF >60 msec above baseline on the 12-lead ECG, confirmed (persistent for >5 minutes) on repeated 12-lead ECGs.
- Evidence of consistent and dose-proportional CDX-7108 systemic absorption, or increase in serum lipase activity. No consistent systemic absorption was demonstrated in preclinical studies, and therefore no exposure cutoff could be defined a priori in relation to the no-observed-adverse-level.

If any of the above subject stopping criteria are met, an unblinded team independent of the SRC may be required to assist in determining whether the AE occurred in the CDX-7108 group. Following review of the safety, tolerability, and available serum PK data, the SRC will make a decision prior to dosing any further subjects to either modify the dose (such as, de-escalating to the previous lower dose level or investigating an intermediate dose level) or stop dosing of all subjects. The final discretion lies with the SRC.

Statistical methods:

<u>Determination of Sample Size:</u>

Given the exploratory nature of this study, the sample size is not based on formal statistical considerations but is typical for FIH studies. Any statistical testing will be considered exploratory and descriptive. In the dose escalation studies, a sample size of 6 subjects per cohort, with a total of 30 subjects in Part A (SAD study) (5 cohorts) and 18 subjects in the Part B (MAD study) (3 cohorts), and a sample size of 10 subjects in Part C (POC study) is expected to be sufficient to meet the objectives of the study.

Analysis Populations:

- Screened Population will include all subjects who sign the informed consent form.
- Randomized Population will include all subjects who are randomized into this study. Subjects will be analyzed according to their randomized treatment, regardless of which treatment the subject received. This population will be used for all summaries of baseline and demographic data.
- Safety Population will include all randomized subjects who receive any amount of the IP. Subjects will be analyzed according to the treatment they actually received, if this differs from that to which the subject is randomized. This population will be used for the summaries of all safety and tolerability data.
- Pharmacokinetic Population will include all randomized subjects who receive any amount of CDX-7108 and have at least 1 evaluable serum PK parameter. Subjects will be analyzed according to the treatment they receive, even if this differs from that to which the subject is randomized. Subjects with dosing deviations that could potentially affect the PK profile will be excluded from the PK Population, at the discretion of the pharmacokineticist.
- Pharmacodynamic Population will include randomized subjects in Part C (POC study) who receive any amount of the IP and have at least 1 evaluable PD result (Pancreo-Lip breath test assessment) at baseline and postdose in both the crossover treatment periods. Subjects will be analyzed according to the treatment they actually received, even if this differs from that to which the subject is randomized.

Safety Analyses:

All safety analyses will be performed on the Safety Population. Adverse events (AEs) will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

All AE summaries will be restricted to treatment-emergent adverse events (TEAEs) only. TEAEs are defined as AEs which commence or worsen in severity on or after the first administration of IP. An overview summary of the frequency and percentage of subjects with TEAEs, as well as number of TEAEs, overall and by TEAE category will be presented by treatment group based on the time of onset of the TEAE and for all subjects. Treatment-emergent AEs will also be grouped by system organ class (SOC) and preferred term (PT) and summarized by treatment group and for all subjects. The TEAEs occurring during the washout period between treatments will be attributed to the last treatment received.

For the summaries of TEAEs, subjects who experience the same TEAE (in terms of the MedDRA SOC and PT) more than once will be only counted once for that event in the number of subjects, but all occurrences of the same event will be counted in the number of events.

Separate summaries will be provided for TEAEs by maximum severity (Mild, Moderate, or Severe) and related TEAEs. Any TEAEs with a missing or unknown severity will be considered as severe in the summary tables.

Treatment-emergent AEs leading to IP discontinuation (for Part B [MAD study] only), TEAEs leading to discontinuation from the study, SAEs, and TEAEs leading to death will be summarized and/or listed separately.

Pharmacokinetic Analyses (Parts A and B only):

Serum CDX-7108 concentrations will be listed for all subjects in the Safety Population. Summaries of serum CDX-7108 concentrations and derived PK parameters will be based on the PK Population.

Serum CDX-7108 concentrations will be listed and summarized using descriptive statistics by treatment group and nominal PK sampling time point. All serum CDX-7108 concentrations that are below the limit of quantification will be labeled as such in the concentration data listings. Individual and arithmetic mean (per treatment) serum concentration-time profiles will also be presented graphically.

Pharmacokinetic parameters of serum CDX-7108 will be listed and summarized by treatment group using descriptive statistics. A regression power model, relating log-transformed maximum concentration (C_{max}) and area under the concentration-time curve (AUC) parameters to log-transformed dose, will be used to

investigate dose proportionality following single-dose and multiple dose administration. Individual and geometric mean C_{max} and AUC parameters will be plotted graphically against dose level. Predose concentration will be summarized for Part B (MAD study).

Analysis of Serum Lipase Activity (Parts A and B only):

Serum lipase activity values will be listed for all subjects in the Safety Population. Summaries of serum lipase activity will be based on the PD Population. Observed values of mean serum lipase activity (%) will be summarized using descriptive statistics at each protocol-scheduled time point and by treatment group. The mean values of serum lipase activity will also be plotted over time by treatment group. An exploratory PK exposure-response analysis may be undertaken to characterize the relationship between CDX-7108 concentrations and serum lipase activity.

Pharmacodynamic Analyses (Part C only):

For Part C (POC study) only, percentage $^{13}CO_2$ excretion rate over baseline (% dose/h), 150_{min} percentage $^{13}CO_2$ excretion rate (% dose/h), and percentage $^{13}CO_2$ cumulative excretion (% dose) will be listed for all subjects in the Safety Population. Descriptive summaries of these parameters will be presented per scheduled-protocol time point and based on the PD Population.

Mean values of the PD parameters will also be plotted over time for each treatment.

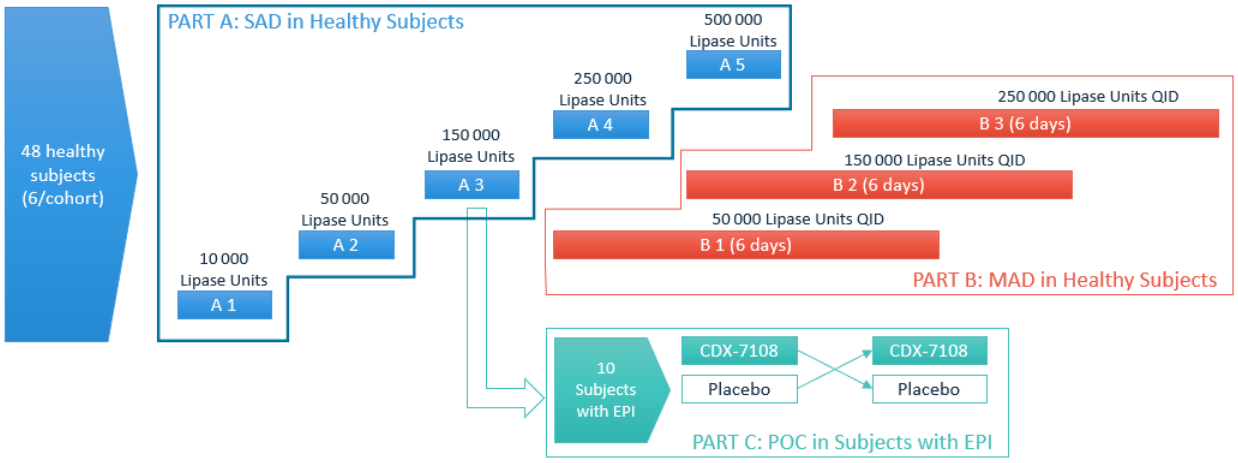
Safety Review Committee:

The SRC will be set up as described in the SRC Charter. The SRC will consist, at a minimum, of the Investigators, an independent Medical Monitor,, and Sponsor/Sponsor's qualified designee(s). The SRC is responsible for reviewing and evaluating the blinded data for the most recently dosed cohort as well as cumulatively obtained data in each part of this study and subsequently at regularly scheduled meetings. The SRC will meet after the completion of each cohort in Part A (SAD study) and Part B (MAD study). The SRC may also meet in ad hoc meetings at its discretion as needed in response to events occurring in the study.

The SRC will be responsible for making recommendations regarding dose escalation/de-escalation, termination of further dose escalation in Part A (SAD study), dose levels to be evaluated in Part B (MAD study) as well as Part C (POC study), requesting unblinding of data, if deemed necessary, and suspension of enrollment, study design modification, or study termination.

1.2 Schema

Figure 1 Study Design and Schema (Parts A, B, and C)



Abbreviations: EPI = exocrine pancreatic insufficiency; MAD = multiple ascending dose; PD = pharmacodynamic; POC = proof-of concept; QID = 4 times a day; SAD = single ascending dose; SRC = Safety Review Committee.
Notes: The CDX-7108 dose levels displayed in Part A (SAD study) are tentative only and are subject to change based on emerging data as determined by the SRC.
The Part B (MAD study) will commence only after the completion of the third single dose cohort (A3) in Part A (SAD study). The dose levels in Part B are subject to change based on the emerging data as determined by the SRC.
The Part C (POC study) will commence after the third single dose cohort (A3) from Part A (SAD study). The dose level of CDX-7108 in Part C is subject to change based on the emerging data from Part A as determined by the SRC.

1.3 Schedule of Activities

1.3.1 Part A

Table 1 Schedule of Assessments for Individual Cohorts – Part A (Single Ascending Dose study)

Study Period	**Screening**		**Treatment and Assessment Period**												**Follow-up Visit**	**EOS/ET**
Study Week	**Weeks −4 to −1**		**Week 1**												**Week 2**	**Week 4**
Study Day	**Days −28 to −2**	**Day −1 (ADM)**	**Day 1 (Dosing Day)**											**Day 2 (DIS) [a]**	**Day 8 (±1 day)**	**Day 22 (±1 day)**
Time Relative to Dose (hour)			**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**24**		
Confinement at study site [a]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Ambulatory visits	X														X	X
Informed consent	X															
Eligibility check	X	X	X													
Demographics	X															
Medical history	X															
Substance use history	X	X														
Height and BMI	X															
Body weight	X														X	X
Physical examination [b]	X	X													X	X
Vital signs [c]	X	X	X			X	X		X		X		X	X		
12-lead ECG [d]	X	X	X				X		X		X		X	X	X	X
Urine drugs screen and alcohol breath test	X	X														
Serology [e]	X															
Serum pregnancy test [f]	X															
Urine pregnancy test [f]		X														X
FSH test [f]	X															
Safety blood laboratory tests [g]	X	X												X	X	X
Urinalysis [g]	X														X	X
Randomization			X													
IP administration with meal (breakfast) [h]				**X**												
PK blood sampling [i]			X		X	X	X	X	X	X	X	X	X	X		
Serum lipase activity [j]			X				X		X							
Anti-CDX-7108 antibody sampling [k]			X												X	X
AE/SAE recording [l]	----------Throughout the study period----------															
Prior and concomitant medications	----------Throughout the study period----------															

Abbreviations: ADM = admission; AE = adverse event; β-hCG = beta human chorionic gonadotropin; BMI = body mass index; COVID-19 = coronavirus disease 2019; DBP = diastolic blood pressure; DIS = discharge; ECG = electrocardiogram; EOS = End-of-Study; ET = early termination; FSH = follicle-stimulating hormone; HAV = hepatitis A virus; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; SBP = systolic blood pressure.

General: At visits when multiple postdose procedures are required to be conducted at the same nominal time point, the following order is recommended: perform vital signs assessments first, followed by ECGs as close as possible to the scheduled time point but prior to PK sampling; perform PK sampling at the scheduled time point; perform other sampling; perform physical examination. All other procedures should be performed as close as possible to the scheduled time point but may be obtained before or after PK sampling.

a. Subjects will be confined to the study site until the morning of Day 2 after collection of the 24-hour postdose samples and study assessments on Day 2.
b. Physical examination will be performed at the indicated time points. A symptom-directed physical examination will be performed at all other visits and at any time throughout the study if required, at the Investigator's discretion (body systems will be reviewed only if clinically indicated).
c. Vital signs include SBP, DBP, pulse rate, respiratory rate, and body temperature. Vital signs will be taken supine or semi-supine after the subject has rested for at least 5 minutes. On Day 1, vital signs will be monitored no more than 1 hour predose and at 30 minutes (±10 minutes), 1 hour (±10 minutes), 2 hours (±10 minutes), 6 hours (±30 minutes), 12 hours (±30 minutes) postdose (after completion of dosing and breakfast); on Day 2, vital signs will be monitored at 24 hours (±60 minutes) postdose.
d. The 12-lead ECGs (in triplicate) will be performed after the subject has rested comfortably in the supine or semi-supine position for at least 5 minutes. On Day 1, ECGs will be performed at 30 minutes predose and at 1 hour (±10 minutes), 2 hours (±10 minutes), 6 hours (±30 minutes), 12 hours (±30 minutes) postdose (after completion of dosing and breakfast); on Day 2, ECGs will be performed at 24 hours (±60 minutes) postdose.
e. Serology tests include HIV, HAV, HBsAg, HBV, HCV, and if required by local health guidelines, COVID-19 testing.
f. Pregnancy tests will be done for women of childbearing potential only; serum β-hCG tests will be performed at Screening and urine pregnancy tests are acceptable at Day -1 and EOS/ET. An FSH test at Screening will be done to determine postmenopausal state in women with unconfirmed reproductive potential status only.
g. Clinical laboratory safety tests include hematology, coagulation, clinical chemistry, and urinalysis. The details of parameters are provided in Appendix 2. Subjects should fast overnight (at least 10 hours) prior to clinical laboratory safety tests at Screening
h. The IP in 30 mL of oral dosing solution including flavored syrup will be administered orally in the morning together with breakfast which should be consumed within 20 minutes of the start of the meal (see Table 7 for details). There are no time restrictions to other meals provided during confinement.
i. Pharmacokinetic samples will be taken within window of at predose (within 10 minutes prior to dosing) and at 15 minutes (±3 minutes), 30 minutes (±3 minutes), 1 hour (±3 minutes), 1.5 hours (±3 minutes), 2 hours (±3 minutes), 4 hours (±3 minutes), 6 hours (±3 minutes), 8 hours (±5 minutes), 12 hours (±5 minutes), and 24 hours (±10 minutes) postdose.
j. Samples for serum lipase activity assessments will be taken on Day 1 at predose (within 10 minutes prior to dosing), and at 1 hour (±3 minutes) and 2 hours (±3 minutes) postdose.
k. Samples for anti-CDX-7108 antibody testing will be taken on Day 1 at 30 minutes predose, at Day 8, and Day 22 (EOS/ET visit).
l. Serious adverse events will be recorded from the time the subject signs the ICF. Reporting of AEs will begin from the time of IP administration.

1.3.2 Part B

Table 2 Schedule of Assessments for Individual Cohorts – Part B (Multiple Ascending Dose Study)

Study Period	**Screening**		**Treatment and Assessment Period**							**Follow-up Visit**	**EOS/ET**
Study Week	**Weeks −4 to −1**		**Week 1**							**Week 3**	**Week 5**
Study Day	**Days −28 to −2**	**Day −1 (ADM)**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6 (EOT)**	**Day 7 (DIS)**	**Day 15 (±1 day)**	**Day 29 (±1 day)**
Confinement at study site [a]		X	X	X	X	X	X	X	X		
Ambulatory visit	X									X	X
Informed consent	X										
Eligibility check	X	X	X								
Demographics	X										
Medical history	X										
Substance use history	X	X									
Height and BMI	X										
Body weight	X									X	X
Physical examination [b]	X	X								X	X
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [d]	X	X	X	X	X	X	X	X	X	X	X
Urine drugs screen and alcohol breath test	X	X									
Serology [e]	X										
Serum pregnancy test [f]	X										
Urine pregnancy test [f]		X									X
FSH test [f]	X										
Safety blood laboratory tests [g]	X	X			X				X	X	X
Urinalysis [g]	X									X	X
Randomization [h]			X								
IP administration with meal [i]			**X**	**X**	**X**	**X**	**X**	**X**			
PK blood sampling [j]			X	X	X	X	X	X	X		
Serum lipase activity [j]			X								
Anti-CDX-7108 antibody sampling [k]			X							X	X
AE/SAE recording [l]	----------Throughout the study period----------										
Prior and concomitant medications	----------Throughout the study period----------										

Abbreviations: ADM = admission; AE = adverse event; β-hCG = beta human chorionic gonadotropin; BMI = body mass index; COVID-19 = coronavirus disease 2019; DBP = diastolic blood pressure; DIS = discharge; ECG = electrocardiogram; EOS = End-of-Study; EOT = End of Treatment; ET = early termination; FSH = follicle-stimulating hormone; HAV = hepatitis A virus; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; MAD = multiple ascending dose; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; SBP = systolic blood pressure.

General: At visits when multiple postdose procedures are required to be conducted at the same nominal time point, the following order is recommended: perform vital signs assessments first, followed by ECGs as close as possible to the scheduled time point but prior to PK sampling; perform PK sampling at the scheduled time point; perform other sampling; perform physical examination. All other procedures should be performed as close as possible to the scheduled time point but may be obtained before or after PK sampling.

a. Subjects will be confined to the study site until the morning of Day 7 (24 hours post-last-dose) after collection of the laboratory samples and study assessments.
b. Physical examination will be performed at the indicated days. A symptom-directed physical examination will be performed at all other visits and at any time throughout the study if required, at the Investigator's discretion (body systems will be reviewed only if clinically indicated).
c. Vital signs include SBP, DBP, pulse rate, respiratory rate, and body temperature. Vital signs will be taken supine or semi-supine after the subject has rested for at least 5 minutes. On Day 1 to Day 6 (dosing days), vital signs will be monitored no more than 1 hour prior to the first dose (breakfast dose) and at 1 hour (±10 minutes) following each dose (after completion of dosing and meal). On Day 7, vital signs will be monitored 12 and 18 hours (±30 minutes) post-last-dose.
d. 12-lead ECGs (in triplicate) will be performed after the subject has rested comfortably in the supine or semi-supine position for at least 5 minutes. On Days 1 to 6 (dosing days), ECGs will be performed no more than 30 minutes prior to the first dose (breakfast dose) and at 1 hour (±10 minutes) following each dose (after completion of dosing and meal). On Day 7, ECGs will be performed 12 and 18 hours (±10 minutes) following the last dose.
e. Serology tests include HIV, HAV, HBsAg, HBV, HCV, and if required by local health guidelines, COVID-19 testing.
f. Pregnancy tests will be done for women of childbearing potential only; serum β-hCG tests will be performed at Screening and urine pregnancy tests are acceptable at Day -1 and EOS/ET. An FSH test at Screening will be done to determine postmenopausal state in women with unconfirmed reproductive potential status only.
g. Clinical laboratory safety tests include hematology, coagulation, clinical chemistry, and urinalysis. The details of parameters are provided in Appendix 2. Subjects should fast overnight (at least 10 hours) prior to clinical laboratory safety tests at Screening.
h. Randomization will be performed on Day 1 predose.
i. The IP in 30 mL of oral dosing solution including flavored syrup will be administered orally at the same time each day (4 times a day, Day 1 to Day 6) together with meals (breakfast, lunch, afternoon snack, and dinner) which should be consumed within 20 minutes of the start of the meal (see Table 7 for details). On dosing days, meals will be provided at regular intervals of 4 hours.
j. Blood samples for PK and serum lipase activity will be collected as per the time points specified in Table 4.
k. Samples for anti-CDX-7108 antibody testing will be taken on Day 1 at 30 minutes prior to first dose (breakfast dose), Day 15, and Day 29 (EOS/ET visit).
l. Serious adverse events will be recorded from the time the subject signs the ICF. Reporting of AEs will begin from the time of IP administration.

1.3.3 Part C

Table 3 Schedule of Assessments for Part C (Proof-of-Concept Study)

Study Period	**Screening**		**Treatment and Assessment Period (Including a 7-day Washout Period)**			**Follow-up Visit**	**EOS/ET**
Study Week	**Weeks −5 to −1**		**Week 1**			**Week 3**	**Week 5**
Study Day	**Days −35 to −2**	**Day −1 (ADM)**	**Day 1 (Treatment 1) (DIS)**	**Day 7 (ADM)**	**Day 8 (Treatment 2) (DIS)**	**Day 15 (±1 day)**	**Day 29 (±1 day)**
Confinement at study site [a]		X	X	X	X		
Ambulatory visit	X					X	X
Informed consent	X					X	X
Eligibility check	X	X	X (predose)				
Demographics	X						
Medical history	X						
Substance use history	X	X					
Height and BMI	X						
Body weight	X					X	X
Physical examination [b]	X	X		X		X	X
Vital signs [c]	X	X	X	X	X	X	X
12-lead ECG [d]	X	X	X	X	X	X	X
Urine drugs screen and alcohol breath test	X	X					
Serology [e]	X						
Serum pregnancy test [f]	X						
Urine pregnancy test [f]		X		X			X
FSH test [e]	X						
Safety blood laboratory tests [g]	X	X		X		X	X
Urinalysis [g]	X					X	X
Randomization			X (predose)				
Standardized meal with ^{13}C-MTG substrate [h]	X						
IP administration with a standardized meal including ^{13}C-MTG substrate [i]			**X**		**X**		
PD assessment (Pancreo-Lip breath test) [j]	X [j]		X		X		
Anti-CDX-7108 antibody sampling [k]			X (predose)			X	X
AE/SAE recording [l]	----------Throughout the study period----------						
Prior and concomitant medications	----------Throughout the study period----------						

Abbreviations: ADM = admission; AE = adverse event; β-hCG = beta human chorionic gonadotropin; BMI = body mass index; COVID-19 = coronavirus disease 2019; DBP = diastolic blood pressure; DIS = discharge; ECG = electrocardiogram; EOS = End-of-Study; EOT = End of Treatment; ET = early termination; FSH = follicle-stimulating hormone; HAV = hepatitis A virus; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; MAD = multiple ascending dose; MTG = mixed triglyceride; PK = pharmacokinetic; SAE = serious adverse event; SBP = systolic blood pressure.

General: At visits when multiple postdose procedures are required to be conducted at the same nominal time point, the Pancreo-Lip breath test procedure should be prioritized and the following order is recommended: perform PD assessment (Pancreo-Lip breath test) first followed by vital signs assessments, ECGs, blood sampling, and lastly, physical examination. All other procedures should be performed as close as possible to the scheduled time point but may be obtained before or after PD assessments.

a. Subjects will be confined to the study site from Day −1 to Day 1 and from Day 7 to Day 8 and will be discharged on Day 1 and Day 8 after completing postdose sampling and study assessments.
b. Physical examination will be performed at the indicated days. A symptom-directed physical examination will be performed at all other visits and at any time throughout the study if required, at the Investigator's discretion (body systems will be reviewed only if clinically indicated).
c. Vital signs include SBP, DBP, pulse rate, respiratory rate, and temperature. Vital signs will be taken supine or semi-supine after the subject has rested for at least 5 minutes. On Day 1 and Day 8, vital signs will be monitored no more than 1 hour predose and at 30 minutes (±10 minutes), 1 hour (±10 minutes), 2 hours (±10 minutes), and 6 hours (±30 minutes) postdose (after completion of dosing and breakfast).
d. The 12-lead ECGs (in triplicate) will be performed after the subject has rested comfortably in the supine or semi-supine position for at least 5 minutes. On Day 1 and Day 8, ECGs will be performed at 30 minutes predose and at 1 hour (±10 minutes), 2 hours (±10 minutes), and 6 hours (±30 minutes) postdose (after completion of dosing and breakfast).
e. Serology tests include HIV, HAV, HBsAg, HBV, HCV, and if required by local health guidelines, COVID-19 testing.
f. Pregnancy tests will be done for women of childbearing potential only; serum β-hCG tests will be performed at Screening and urine pregnancy tests are acceptable at Day -1 and EOS/ET. An FSH test at Screening will be done to determine postmenopausal state in women with unconfirmed reproductive potential status only.
g. Clinical laboratory safety tests include hematology, coagulation, clinical chemistry, and urinalysis. The details of parameters are provided in Appendix 2. Subjects should fast overnight (at least 10 hours) prior to clinical laboratory safety tests at Screening.
h. At Screening, subjects will receive a standardized meal consisting of 1 slice of toast with 10 g of butter and 10 g of a chocolate cream (Nutella®, Ferrero, Germany) mixed with ^{13}C-MTG substrate, which should be consumed within 10 minutes of the start of the meal (Section 5.3.1). The meal can be accompanied with 150 mL of black coffee, tea, or still water. Thereafter, no food should be allowed for at least 4 hours following dosing and breakfast. Further drinks are not allowed until the end of the breath test, with the exception of a small amount of water (<100 mL).
i. The IP in 30 mL of oral dosing solution including flavored syrup will be administered orally at the same time on Day 1 and Day 8 together with the standardized meal including ^{13}C-MTG substrate (Section 5.3.1), which should be consumed within 10 minutes of the start of the meal (see Table 7 for details).
j. Breath samples (Section 8.8.1) will be collected at Screening (as close to Day −35 as possible) and on Days 1 and 8 at the time points specified in Table 5. Subjects will be required to fast overnight (for at least 10 hours) prior to the Pancreo-Lip breath test.
k. Samples for anti-CDX-7108 antibody testing will be taken on Day 1 at 30 minutes prior to Treatment 1, at Day 15, and Day 29 (EOS/ET visit).
l. Serious adverse events will be recorded from the time the subject signs the ICF. Reporting of AEs will begin from the time of IP administration.

1.3.4 Pharmacokinetic, Serum Lipase Activity, and Pharmacodynamic Assessment Time Windows

Table 4 Blood Sampling Time Points for Pharmacokinetic and Serum Lipase Activity Assessments – Part B (MAD study)

Study Day	Time point relative to dosing	Allowed window	PK	Serum Lipase Activity
Day 1	Prior to first dose (breakfast dose)	Within 10 min prior to dosing	X	X
	30 minutes post each dose	±3 min	X	
	1 hour post each dose	±3 min	X	X
	1.5 hours post each dose	±3 min	X	
	2 hours post each dose	±3 min	X	X
	4 hours post each dose (sample to be collected before the next dose)	±3 min	X	
Day 2 to Day 6	Prior to first dose (breakfast dose)	Within 10 min prior to dosing	X	
	1 hour post each dose [a]	±3 min	X	
Day 7	12 hours post-last-dose on Day 6	±5 min	X	
	18 hours post-last-dose on Day 6	±10 min	X	

Abbreviations: MAD = multiple ascending dose; PK = pharmacokinetics; SAD = single ascending dose; T_{max} = time to maximum serum concentration.

Notes: Postdose refers to the end of dosing and the meal.

The PK sampling time points are subject to change based on emerging data from Part A (SAD study).

a. This time point may be revised to coincide with the estimated T_{max} based on emerging data from Part A (SAD study).

Table 5 Procedure and Breath Sampling Time Points for Pharmacodynamic (Pancreo-Lip MTG Breath Test) Assessments – Part C (POC study)

Study Day	Time point relative to dosing	Allowed window	Procedure/Number of Breath Samples
Screening [a]	10 minutes predose	±3 min	1st and 2nd breath sample taken one after the other (a total of 2 baseline breath samples)
	Standardized meal (0 h)	-	See Section 5.3.1 for details
	30 minutes postdose	±3 min	3rd breath sample
	60 minutes (1 hour) postdose	±3 min	4th breath sample
	90 minutes (1.5 hours) postdose	±3 min	5th breath sample
	120 minutes (2 hours) postdose	±3 min	6th breath sample
	150 minutes (2.5 hours) postdose	±3 min	7th breath sample
	180 minutes (3 hours) postdose	±3 min	8th breath sample
	210 minutes (3.5 hours) postdose	±3 min	9th breath sample
	240 minutes (4 hours) postdose	±3 min	10th breath sample (last measurement)
Day 1 and Day 8	10 minutes predose	±3 min	1st and 2nd breath sample taken one after the other (a total of 2 baseline breath samples)
	Dosing with standardized meal (0 h)	-	Receive CDX-7108 or placebo in 30 mL of oral dosing solution including flavored syrup together with a standardized meal (Section 5.3.1), which should be consumed within 10 minutes of the start of the meal (see Table 7 for details).
	30 minutes postdose	±3 min	3rd breath sample
	60 minutes (1 hour) postdose	±3 min	4th breath sample
	90 minutes (1.5 hours) postdose	±3 min	5th breath sample
	120 minutes (2 hours) postdose	±3 min	6th breath sample
	150 minutes (2.5 hours) postdose	±3 min	7th breath sample

Study Day	Time point relative to dosing	Allowed window	Procedure/Number of Breath Samples
	180 minutes (3 hours) postdose	±3 min	8th breath sample
	210 minutes (3.5 hours) postdose	±3 min	9th breath sample
	240 minutes (4 hours) postdose	±3 min	10th breath sample (last measurement)

Abbreviations: MTG = mixed triglyceride; POC = proof-of-concept.

Note: Postdose refers to the end of dosing and the meal.

a. The Screening MTG breath test should be done as close to Day −35 as possible.

2.0 INTRODUCTION

2.1 Background

Exocrine pancreatic insufficiency (EPI) is a deficiency of the pancreatic enzymes within the intestinal lumen, resulting in maldigestion and malabsorption.[1] Symptoms of EPI include mild abdominal discomfort, bloating, cramping, and increased flatulence. Patients with severe insufficiency have steatorrhea and weight loss. The most common causes of EPI are chronic pancreatitis (CP), pancreatic cancer, cystic fibrosis (CF), diabetes mellitus, and celiac disease. Other less frequent causes are short bowel syndrome, hereditary hemochromatosis, and Zollinger-Ellison syndrome. Up to 85% of patients with advanced CP have EPI.[2] The CP patients present chronic abdominal pain and exocrine or endocrine dysfunction, and present pancreatic atrophy, ductal changes, and calcification in the imaging.[3] The EPI is near universal in patients with locally advanced or metastatic pancreatic cancer, with as high as 90% to 100% of patients affected.[4] Additionally, patients with cystic fibrosis have dysfunctional secretion of pancreatic enzymes as a result of mutations in the CF transmembrane conductance regulator gene and pancreatic insufficiency is the most common gastrointestinal (GI) complication of CF affecting approximately 80% of CF patients.[5]

The mainstay of treatment for EPI is pancreatic enzyme replacement therapy (PERT), which is a life-long requirement for a majority of EPI patients. In addition to PERT, lifestyle changes, especially stopping smoking and drinking alcohol, are necessary in the management of patients with EPI.[1] The PERT aims to supplement at least 10% of estimated pancreatic lipase to correct steatorrhea and improve digestion.[2] It has been demonstrated that at least 30 000 IU (or about 90 000 United States Pharmacopoeia [USP] units) of lipase delivered to the intestine with each meal is generally needed to eliminate steatorrhea.[1,5,6] All currently available PERT are derived from porcine pancreas. The PERT formulations can be enteric coated and non-enteric coated. The enteric coated formulations are generally preferred over the non-enteric coated ones since the non-enteric coated PERT requires the concomitant administration of proton-pump inhibitors (PPI) or histamine-2 blockers (H2B) to prevent enzyme denaturation in the stomach.

Several factors determine the response to treatment, including degree of residual pancreatic function, anatomy, and the size and fat content of meals.[1,5] Because of differences in remaining pancreatic secretion and gastric production of lipase, PERT therapy must be tailored to the individual patient, based on severity of symptoms and response to treatment.[1]

Consistently achieving high levels of adherence to PERT is also a considerable challenge. The most common reason for PERT treatment failure is inadequate dosage. Either the patient requires more enzyme or the intake timing is incorrect, resulting in inadequate mixing of enzymes with chyme in the duodenum. When high PERT doses are needed, prescribing higher strength capsules will reduce pill burden and improve compliance. [5] However, in very severe EPI patients the pill burden can remain a serious problem despite of the use of high strength capsules.

2.2 CDX-7108, a Recombinant Lipase

CDX-7108, an oral recombinant lipase developed by Codexis, Inc, is being investigated by Nestlé Health Science (hereafter, the Sponsor) for the treatment of EPI. It is a modified version of a triacylglycerol lipase enzyme derived from the bacteria *Bacillus thermoamylovans* (btLIP) and produced by fermentation of recombinant *Escherichia coli*.[7]

CDX-7108 is resistant to gastric pH and therefore does not require enteric coating, and exhibits lipolytic activity comparable to porcine PERT in considerably smaller amounts. These characteristics represent the basis for the development of a new totally or partially synthetic PERT that could outperform existing porcine derived products in terms of efficacy and treatment compliance.

In vitro studies indicated an improved stability of CDX-7108 to intestinal proteases, acidic conditions, pepsin, and elevated temperatures, while retaining enzymatic activity on broad spectrum of dietary fats. In vivo pharmacology efficacy studies demonstrated the ability of CDX-7108 to increase the coefficient of fat absorption and decrease the amount of fat in fecal material from pancreatic duct-ligated minipigs. Furthermore, CDX-7108 showed equal efficacy to CREON®, an approved porcine PERT for the treatment of EPI which contains lipase, protease, and amylase, at a dose that was approximately a third lower based on unit specific activity.

CDX-7108 is poorly and variably absorbed when administered in Sprague Dawley rats (28-day oral toxicity study) at doses up to 369 mg/kg/day. The CDX-7108 absorption was also poor in cynomolgus monkeys following oral administration 3 times a day for 28 days. The Day 1 serum exposure (C_{max} and AUC) of CDX-7108 in cynomolgus monkeys increased as the dose increased. There was no evidence of CDX-7108 accumulation with repeated exposure.

In Good Laboratory Practice (GLP) compliant safety and toxicity studies in Sprague Dawley rats and cynomolgus monkeys, oral administration of CDX-7108 was well tolerated in both species at doses up to and including 369 mg/kg following 28-days of dosing. No adverse effects were reported for any measured parameter including body weight, body weight gain, food consumption, clinical pathology (hematology, coagulation, clinical chemistry, and urinalysis), ophthalmology, or electrocardiography (monkeys only). Furthermore, no CDX-7108-related macroscopic or microscopic findings of all standard tissues, were evident in the necropsy after dosing was terminated on Day 28 or in the recovery groups on Day 43 in either species at doses up to 369 mg/kg/day. Therefore, oral administration at a dose level of 369 mg/kg/day of CDX-7108 (CDX-7108 concentration of up 29.4 mg/mL) for 28 consecutive days of dosing was considered as the no-observed-adverse-effect level (NOAEL) in both rats and monkeys.

2.3 Study Rationale

No clinical studies have yet been performed with CDX-7108 and its effects in humans are unknown. This is the first-in-human (FIH) study of CDX-7108, which aims to assess the safety, tolerability, and pharmacokinetics (PK) of escalating single and multiple doses of CDX-7108 in healthy subjects, and proof of concept (POC) via the pharmacodynamics (PD) of a single dose of CDX-7108 in subjects with EPI.

The study hypotheses are:

- CDX-7108 is safe and well tolerated when administered with food at single and multiple ascending oral doses in healthy volunteers and at a single therapeutic dose in subjects with EPI.
- CDX-7108 is not, or only minimally, absorbed after oral administration (ie, no clinically relevant systemic exposure) and a single therapeutic dose of CDX-7108 is able to improve lipid absorption in subjects with EPI.

2.4 Benefit/Risk Assessment

As the single ascending dose (SAD)/multiple ascending dose (MAD) part of the study will be conducted in healthy human subjects and the POC part of the study will involve the administration of a single therapeutic dose of CDX-7108 to EPI patients, a health benefit to subjects is not anticipated.

Based on the findings in animal studies, CDX-7108 was safe and well tolerated with no potential risks identified. In this FIH study, a series of safety examinations will be completed to monitor the health status of the subjects during the study. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of CDX-7108 may be found in the current Investigator's Brochure (IB).[7]

The clinical study protocol has been designed such that the risk to subjects in this study will be minimized by adequate selection of eligibility criteria, and schedule of clinical monitoring, in house observation, administration, and treatment duration. The Sponsor will immediately notify the Investigator if any additional safety or toxicology information becomes available during the study.

During an ongoing global pandemic such as coronavirus disease 2019 (COVID-19), there may be inherent risks with travel to and attendance of on-site visits. Subjects will be encouraged to follow the guidance of local health authorities and the local site standard operating procedures (SOPs) in these instances. Details of COVID-19 risk mitigation procedures during the study will be addressed separately.

This study will be performed in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements. Aspects of the study concerned with the investigational product (IP) will meet the local regulatory requirements in New Zealand and Australia and Good Manufacturing Practice (GMP) guidelines.

3.0 OBJECTIVES AND ENDPOINTS

Table 6 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety, and tolerability of single and multiple ascending oral doses of CDX-7108 in healthy subjects, as well as of a single therapeutic dose in subjects with EPI.	• The safety parameters to be assessed include AEs/SAEs and changes in clinical laboratory tests, vital signs, 12-lead ECG, and physical examination from baseline
Secondary	
• To characterize the PK profile of single and multiple ascending oral doses of CDX-7108 when administered with food in healthy subjects.	• Serum concentration-time profile of CDX-7108 • The serum PK parameters include: o Part A (SAD): AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and $t_{1/2}$ o Part B (MAD): $AUC_{0-\tau}$, AUC_{0-t}, $C_{ss,max}$, Day 1 to Day 6 C_{τ} (predose), T_{max}, and $t_{1/2}$
• To exclude changes in overall serum lipase activity after administration of single and multiple ascending oral CDX-7108 when administered with food in healthy subjects.	• Serum lipase activity
• To explore the preliminary PD of a single therapeutic dose of CDX-7108 in subjects with EPI as assessed by measurement of lipid absorption (Pancreo-Lip® breath test).	• The PD parameters of CDX-7108 include: o Percentage $^{13}CO_2$ excretion rate over baseline (% dose/h) o 150_{min} percentage $^{13}CO_2$ excretion rate (% dose/h) o Percentage $^{13}CO_2$ cumulative excretion at 240 minutes (% dose)
Tertiary	
• To evaluate immunogenicity of single and multiple ascending oral doses of CDX-7108 in healthy subjects, as well as of a single therapeutic dose in subjects with EPI.	• Development of anti-CDX-7108 antibodies

Abbreviations: AE = adverse event; AUC_{0-inf} = area under the concentration-time curve from time zero to infinity; AUC_{0-t} = area under the concentration-time curve from time zero to the last sampling time; $AUC_{0-\tau}$ = area under the concentration-time curve over the dosing interval (τ) at steady state; C_{max} = maximum serum concentration; $C_{ss,max}$ = maximum concentration at steady sate; C_{τ} = predose concentration over the dosing interval (τ); $^{13}CO_2$ = carbon dioxide; ECG = electrocardiogram; EPI = exocrine pancreatic insufficiency; MAD = multiple ascending dose; PD = pharmacodynamic; PK = pharmacokinetic; SAD = single ascending dose; SAE = serious adverse event; T_{max} = time to maximum serum concentration; $t_{1/2}$ = terminal elimination half-life.

4.0 STUDY DESIGN

4.1 Overall Design

This is an integrated 3-part study to investigate the safety, tolerability, PK, and PD of CDX-7108. The Parts A and B are randomized, double-blind, placebo-controlled dose-escalation parts to investigate the safety, tolerability, immunogenicity, and PK of CDX-7108 after single and multiple oral dose administration in healthy adult subjects. Part C is a randomized, double-blind, placebo-controlled, single-dose, 2-way crossover part to assess POC of CDX-7108 in terms of PD as well as safety, tolerability, and immunogenicity in subjects with EPI. The study will commence with Part A (SAD study) and will progress to Part B (MAD study) and Part C (POC study) as described below. A study schema is provided in Figure 1.

Approximately 58 subjects will be enrolled at multiple sites in New Zealand and Australia. Approximately 48 adult healthy male and female subjects will be enrolled in at least 5 cohorts in Part A (SAD study) and up to 3 cohorts in Part B (MAD study). Each cohort in Parts A and B will include 6 subjects (4 receiving CDX-7108 and 2 receiving placebo) with at least 2 male and 2 female subjects. Approximately 10 subjects with severe EPI will be enrolled in Part C (POC study) of the study.

Each subject in Parts A and B will be enrolled in only 1 cohort and receive only one dose regimen in this study. Dosing will be escalated in a sequential fashion, contingent on a review of safety, tolerability, and available PK data of the previous dose level by a Safety Review Committee (SRC) (see Section 4.5 for details). The proposed dose levels/dosing frequency of CDX-7108 may be adjusted over the course of the study and cohorts may be added if it is deemed appropriate or necessary by the SRC to repeat a dose level in a new cohort of subjects or to study an interim dose level or cohorts may be removed depending on the emerging safety, tolerability, and available PK data.

4.1.1 Part A (Single Ascending Dose Study)

In the SAD study, a total of approximately 30 subjects will be enrolled in up to 5 sequential cohorts, which will evaluate single-dose administration of CDX-7108 at the following anticipated dose levels: 10 000, 50 000, 150 000, 250 000, and 500 000 lipase units (Figure 1). Based on the emerging data, intermediate or lower dose levels of CDX-7108 may be explored at the discretion of the Sponsor in consultation and agreement with the Investigator and SRC.

The study duration per subject will be approximately 7 weeks (including Screening). The study will consist of a 28-day (4-week) Screening period, and a 22-day (approximately 3 weeks) treatment and assessment period.

Subjects will undergo a Screening visit between Day −28 and Day −1 to determine their eligibility for the study. Subjects who meet the eligibility criteria will be admitted to the study

site on the day prior to dosing (Day −1), during which their continued eligibility will be assessed up to Day 1 prior to dosing. Subjects will be randomized on Day 1 and will receive a single oral dose of CDX-7108 or matched placebo in 30 mL of oral dosing solution including flavored syrup together with a standard breakfast, which should be consumed at the study site within 20 minutes of the start of the meal.

Within each cohort, safety, tolerability, PK, and serum lipase activity assessments will be performed at predefined time points as specified in the Schedule of Assessments (Table 1). Subjects will remain at the study site for observation up to the morning of Day 2 after all 24-hour postdose assessments have been performed and samples collected and will be discharged thereafter. Subjects will return to the study site on an outpatient basis on Day 8 for a Follow-up visit and then on Day 22 for the End-of-study (EOS) visit. The EOS visit will also be the early termination (ET) visit if required.

4.1.1.1 Sentinel Dosing

As this is a FIH study, a sentinel dosing strategy will be employed for each dose cohort in the SAD study. Each cohort will include 2 sentinel subjects (1 CDX-7108, 1 placebo) who will be dosed first and monitored by the Investigator for a minimum of 24 hours prior to dosing the rest of the cohort. Once the dose is deemed to be safe and well tolerated (as defined by a lack of initial acute AEs that meet the study stopping criteria specified in Section 4.7) in the sentinel subjects by the Investigator, in consultation with the independent Medical Monitor and Sponsor as needed, the remaining 4 subjects in the cohort (3 CDX-7108, 1 placebo) will be administered the IP without the requirement of a formal SRC decision. The decision to dose the rest of the cohort will be documented.

4.1.2 Part B (Multiple Ascending Dose Study)

In the MAD study, approximately 18 subjects will be enrolled in up to 3 sequential cohorts, which will evaluate multiple dose administration of CDX-7108 at an appropriate low (50 000 lipase units), mid (150 000 lipase units), and high dose (250 000 lipase units) 4 times a day (QID) for 6 consecutive days (Figure 1). Part B (MAD study) will commence only after the completion of the third single-dose cohort (150 000 lipase units) in Part A (SAD study) and following SRC review of the data from this cohort. Dose level decisions for Part B (MAD study) will be guided by the emerging safety, tolerability, and PK data from Part A (SAD study) as well as from Part B (MAD study).

The study duration per subject will be approximately 8 weeks (including Screening). The study will consist of a 28-day (4-week) Screening period, a 6-day treatment period, and a 3-week post-treatment follow-up period.

Subjects will undergo a Screening visit between Day −28 and Day −1 to determine their eligibility for the study. Subjects who meet the eligibility criteria will be admitted to the study

site on the day prior to dosing (Day −1), during which their continued eligibility will be assessed up to Day 1 prior to dosing. Eligible subjects will be randomized on Day 1 and will receive an oral dose of CDX-7108 or placebo QID in 30 mL of oral dosing solution including flavored syrup from Day 1 to Day 6 together with a meal (breakfast, lunch, afternoon snack, or dinner), which should be consumed within 20 minutes of the start of the meal. Meals will be provided at regular intervals of 4 hours.

Within each cohort, safety, tolerability, PK, and serum lipase activity assessments will be performed at predefined time points as specified in the Schedule of Assessments (Table 2). Subjects will remain at the study site for observation up to the afternoon of Day 7 (18 hours post-last-dose) and will be discharged after all assessments have been performed and samples collected. Subjects will return to the study site on an outpatient basis on Day 15 for a Follow-up visit and then on Day 29 for an EOS visit. The EOS visit will also be the ET visit if required.

4.1.3 Part C (Proof-of-Concept Study)

Part C (POC study) of the study is designed as 2-way crossover design with a 7-day washout period. A total of 10 subjects with severe EPI from partial/total pancreatectomy or CP will be enrolled. It is anticipated that Part C (POC study) will commence after completion of the third single-dose cohort (150 000 lipase units) from Part A (SAD study) and following SRC review of the data from this cohort; this dose level is expected to be therapeutically active in subjects with severe EPI. However, a different dose level could be selected depending on emerging safety, tolerability, and PK data from Part A (SAD study).

The study duration per subject will be approximately 9 weeks (including Screening). The study will consist of a 35-day (5-week) Screening period, an 8-day treatment and assessment period including 2 dosing days separated by a washout of 7 days, and a 3-week post-treatment follow-up period (Table 3).

Subjects will undergo Screening between Day −35 and Day −1 to determine their eligibility for the study; screening procedures will include a Pancreo-Lip® breath test following consumption of a standardized meal containing ^{13}C-mixed triglyceride (MTG) substrate to confirm the subjects' severe EPI status. Subjects who meet the eligibility criteria will be admitted to the study site on the day prior to dosing (Day −1), during which their continued eligibility will be assessed up to Day 1 prior to dosing. Subjects will be randomized in a 1:1 ratio to one of the 2 treatment sequences: CDX-7108→placebo or placebo→CDX-7108 on Day 1. Following an overnight fast on Day 1 and Day 8, subjects will not receive their usual PERT but instead will receive a single oral dose of CDX-7108 or matched placebo in 30 mL of oral dosing solution including flavored syrup together with a standardized breakfast containing ^{13}C-MTG substrate, which should be consumed within 10 minutes of the start of the meal. Thereafter subjects will remain fasted for at least 4 hours for the Pancreo-Lip breath test, after which food accompanied by their usual PERT will be permitted.

Pharmacodynamic assessments using a Pancreo-Lip breath test, as well as safety and tolerability assessments will be performed at predefined time points as specified in the Schedule of Assessments (Table 3 and Table 5). Following dosing on Day 1, subjects will remain at the study site for observation and collection of postdose samples and will be discharged the same day. Subjects will then return to the study site on Day 7 and will remain at study site until Day 8 for postdose samples and will be discharged thereafter. Subjects will visit the study site on an outpatient basis on Day 15 for a Follow-up visit and then on Day 29 for an EOS visit. The EOS visit will also be the ET visit if required.

4.2 Scientific Rationale for Study Design

This is a FIH, 3-part, randomized, SAD/MAD and POC study of CDX-7108 in healthy subjects and subjects with severe EPI.

The Part A (SAD study) and Part B (MAD study) of the study will be performed in healthy subjects to characterize the safety, tolerability, and PK of CDX-7108 in humans in the absence of any disease-related and potentially confounding factors. The Part C (POC study) will be conducted in subjects with EPI to detect the signal of efficacy of CDX-7108 in the target patient population in addition to safety and tolerability. The inclusion criteria were chosen to help ensure the inclusion of only healthy subjects for Parts A (SAD study) and B (MAD study), and subjects with severe EPI for study Part C (POC study). Additional criteria are in place to ensure the safety and wellbeing of subjects.

Use of a placebo control will help distinguish any potential effects between CDX-7108 itself and other effects not related to CDX-7108 with minimal bias. A 4:2 ratio of CDX-7108 versus placebo in the dose escalation studies and 1:1 ratio in the POC crossover study is deemed to an acceptable standard used in FIH studies.

As per common practice for Phase 1 studies, subjects will remain confined to the study site during the dosing period in all study parts. In addition, as this is a FIH study, a sentinel dosing strategy will be employed for the first 2 subjects in each dose cohort in Part A (SAD study) followed by a review of blinded safety data up to 24 hours after dosing to rule out any initial, severe, or acute reactions. An observation and confinement period up to a maximum of 24 hours is considered appropriate, considering no accumulation of CDX-7108 following repeated administration in nonclinical PK studies. Furthermore, because the planned dose levels to be studied in Part A (SAD study) are aimed to also cover the dose levels to be studied in Part B (MAD study) and Part C (POC study), the lack of sentinel dosing in Parts B and C is considered to be justified.

The study is randomized and double-blinded to minimize bias arising from the assignment of subjects to treatment groups, and the expectations of subjects, Investigators, and individuals collecting data. In Part C (POC study), 2-way crossover allocation was chosen for greater latitude of the statistical requirement to resolve any treatment effect.

In Part A (SAD study), a step-wise single-dose escalation will be used to evaluate safety, and PK of CDX-7108 with minimal risk to subjects. A low starting dose is used to evaluate safety with minimal risk, and sentinel subjects will be dosed for each SAD cohort. The study design is adaptive, allowing changes to the proposed dose levels if needed, with a maximum dose of 500 000 lipase units to be evaluated to ensure satisfactory review of single-dose safety, tolerability, and PK. This approach will support confirmation or modification of the most suitable doses for investigation in Part B (MAD study) and in Part C (POC study).

In Part B (MAD study), a step-wise multiple dose escalation will be used to evaluate the safety, tolerability, and PK of multiple doses of CDX-7108. The study design is also adaptive, allowing changes to the proposed dose levels if needed, to ensure satisfactory review of multiple dose safety, tolerability, and PK. The dosing duration of 6 days was primarily chosen to allow for the adequate assessment of the PK (including evaluation of steady state PK) within the study. Results from the 5-day and 28-day study in rat and monkey suggested that a 6-day dosing duration of CDX-7108 is applicable. Furthermore, this duration anticipates the standard treatment exposure of approximately 6 to 7 days to appropriately assess efficacy in Phase 2.

To mitigate risks, dose escalation stopping criteria have been defined covering safety, liver chemistry, and electrocardiogram (ECG) parameters, as well as maximum serum PK exposure limits.

All assessments proposed in this study are considered by the Sponsor to be appropriate and necessary to obtain the required safety, tolerability, PK, and PD data for CDX-7108. In addition, serum lipase activity assessment will serve as an indirect measurement of PK, to confirm the lack of systemic exposure following administration of CDX-7108. The Pancreo-Lip test (^{13}C-MTG breath test) is a standard test for the indirect measurement of fat absorption within the small intestine which serves as an index of exocrine pancreatic malfunction and will be used as a measure of CDX-7108 response in subjects with EPI in Part C (POC study).

4.3 Justification for Dose

The doses of CDX-7108 intended to be tested in this FIH study are from 10 000 to 500 000 lipase units as single dose administration and from 50 000 to 250 000 lipase units as multiple dose administration. Using the per-label porcine PERT dosing range as a reference,[8] 10 000 lipase units is below the therapeutic level and was considered appropriate as the starting dose in Part A (SAD study). The 150 000 to 250 000 lipase unit range of doses selected for Part B (MAD study) was also considered appropriate as it covers and slightly exceeds the porcine PERT therapeutic dose range.

A single dose of 150 000 lipase units is intended to be administered to subjects with EPI. This dose is expected to be in the therapeutic range of commercially available porcine PERT, but below the maximum per-label dose.[8]

In line with United States Food and Drug Administration guidance,[9] the maximum recommended starting dose for this study was calculated from an estimated human equivalent dose, based on the NOAELs from formal GLP 28-day repeated-dose toxicity studies in rats and monkeys. Based on the nonclinical toxicology results, oral administration via gavage at a dose level of 369 mg/kg/day of CDX-7108 (CDX-7108 concentration of up 29.4 mg/mL) for 28 consecutive days of dosing was considered as the NOAEL in both rats and monkeys. On a mg/kg basis, this represents approximately a 30-fold margin of safety compared to the proposed high doses to be used in this study.

4.4 Study Completion and End of Study Definition

For each study part, a subject is considered to have completed the study if he/she has completed all periods of the study including the last visit (EOS visit) and the last scheduled procedure, as shown in the Schedule of Activities (Table 1, Table 2, and Table 3).

The end of the study is defined as the date of the last visit of the last subject in the study.

4.5 Safety Review Committee

The SRC will be set up as described in the SRC Charter. The SRC will consist, at a minimum, of the Investigators, an independent Medical Monitor, and Sponsor/Sponsor's qualified designee(s).

The SRC is responsible for reviewing and evaluating the blinded data for the most recently dosed cohort as well as cumulatively obtained data in dose escalation parts of this study (as specified in Section 4.6) and subsequently at regularly scheduled meetings. The SRC will meet after the completion of each cohort in Part A (SAD study) and Part B (MAD study). The SRC may also meet in ad hoc meetings at its discretion as needed in response to events occurring in the study.

The SRC will be responsible for making recommendations regarding the following:

- Dose escalation/de-escalation.
- Termination of further dose escalation in Part A (SAD study) if it is expected that further escalation will not be tolerated or if it is determined that a maximum exposure may be reached (Section 4.7).
- The respective dose levels to be evaluated in Part B (MAD study).
- The dose level to be evaluated in Part C (POC study).
- Request unblinding of data, if deemed necessary.
- Suspension of enrollment, study design modification, or study termination.

4.6 Dose Escalation Criteria

There will be no intrasubject dose escalation (ie, the same IP dose will be administered to each subject within a cohort).

For both Part A (SAD study) and Part B (MAD study), dose escalation to the next dose level(s) will not proceed until the previous dose level has been deemed safe and well tolerated by the SRC (ie, none of the stopping criteria specified in Section 4.7.2 are met). There will be a minimum of 22 days between dosing of each SAD cohort and a minimum of 29 days between dosing of each MAD cohort to permit a timely review and evaluation of emerging data by the SRC prior to proceeding to the next higher dose level.

For each completed cohort in Part A (SAD study) and Part B (MAD study), all data (safety, tolerability, and serum PK data) for all dosed subjects through to Day 8 in Part A (SAD study) and through to Day 15 in Part B (MAD study), as well as cumulative data across the completed cohorts, will be reviewed by the SRC prior to dose escalation. The SRC review dataset will, at minimum, consist of any AEs, laboratory test results (hematology, coagulation, clinical chemistry, and urinalysis), flagged vital signs, ECG data, and serum PK data (concentration-time profiles, and PK parameters of C_{max} [or $C_{ss,max}$ as appropriate] and AUC). The PK data will be de-identified to maintain the blind.

If, based on the emerging data, the SRC considers that the next higher dose level may not be tolerated, the SRC may decide to de-escalate to the previous lower dose level or investigate an intermediate dose level.

4.7 Study Stopping Criteria

4.7.1 Stopping Criteria for Individual Subjects

In Part B (MAD study), dosing for any individual subject will be stopped if:

- The subject experiences a serious adverse event (SAE) or a clinically significant and IP-related AE, which in the opinion of the PI, Medical Monitor, and Sponsor, warrants discontinuation of the study for that subject's wellbeing.
- Evidence of consistent and dose proportional CDX-7108 systemic absorption, or increase in serum lipase activity. No consistent systemic absorption was demonstrated in preclinical studies, and therefore no exposure cutoff could be defined a priori in relation to the no-observed-adverse-level.

4.7.2 Criteria for Pausing/Stopping Dose Escalation

If any of the following scenarios occur, dose escalation may be paused/stopped. If any of the below criteria are met in Part A (SAD study), then progression to Part B (MAD study) will occur only at dose levels deemed to be safe and well tolerated in Part A.

- ≥1 subject experiences SAEs considered to be related to the IP.
- ≥2 subjects experience severe AEs of the same character considered to be related to the IP.
- ≥1 subject meets 1 of the following liver chemistry stopping criteria in alignment with the United States Food and Drug Administration premarketing clinical liver safety guidance:[10]

  - Alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) (or ALT ≥3 × ULN and international normalized ratio [INR] >1.5), termed "Hy's Law". This event must be reported as an SAE
  - ALT ≥5 × ULN
  - ALT ≥3 × ULN, if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity (such as fatigue, nausea, vomiting, pain, or tenderness in the right upper quadrant, fever, rash, or eosinophilia)

  Refer Appendix 4 for suggested actions and follow-up of events related to liver safety.

- ≥2 subjects who receive the IP have a QTc prolongation defined as QT interval corrected for heart rate using Fridericia's formula (QTcF) >500 msec, or an increase of QTcF >60 msec above baseline on the 12-lead ECG, confirmed (persistent for >5 minutes) on repeated 12-lead ECGs.
- Evidence of consistent and dose proportional CDX-7108 systemic absorption, or increase in serum lipase activity. No consistent systemic absorption was demonstrated in preclinical studies, and therefore no exposure cutoff could be defined a priori in relation to the no-observed-adverse-level.

If any of the above subject stopping criteria are met, an unblinded team independent of the SRC may be required to assist in determining whether the AE occurred in the CDX-7108 group. Following review of the safety, tolerability, and available serum PK data, the SRC will make a decision prior to dosing any further subjects to either modify the dose (such as, de-escalating to the previous lower dose level or investigating an intermediate dose level) or stop dosing of all subjects. The final discretion lies with the SRC.

4.7.3 Criteria for Pausing/Stopping the Study

If any of the above criteria for stopping dose escalation (Section 4.7.2) are met in either Part A (SAD study) or Part B (MAD study), the study may be stopped. This decision will be made by the SRC.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if ALL of the following criteria specific to Parts A, B, and C apply at any time starting from Screening up to Day 1 prior to IP administration:

5.1.1 All Subjects

1. Capable of giving signed informed consent prior to initiation of any protocol-specific procedures as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Body mass index (BMI) between 18.0 and 30.0 kg/m^2.
3. Nonsterilized male subjects are eligible to participate if they agree to ONE of the following starting at Screening and continuing throughout the clinical study period, and for 90 days after IP administration:
    a. Must agree to stay abstinent (where abstinence is the preferred and usual lifestyle of the subject), OR
    b. Male subjects with a female partner of childbearing potential must agree to use highly effective contraception consisting of 2 forms of birth control (1 of which must be a barrier method, as defined in Appendix 3).
    c. Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.
    d. These requirements do not apply to subjects in a same sex relationship.
4. Male subjects must agree not to donate sperm starting at Screening and continuing throughout the clinical study period, and for 90 days after IP administration.
5. Female subjects of childbearing potential are eligible to participate if they meet the following criteria:
    a. Must agree not to become pregnant during the clinical study period and for 30 days after IP administration.
    b. Must have a negative serum pregnancy test at Screening and Day −1.
    c. If heterosexually active, must agree to consistently use a form of highly effective birth control, in combination with a barrier method (as defined in Appendix 3) starting at Screening (signing the ICF) and continuing throughout the clinical study period, and for 30 days after IP administration, OR
    d. Must agree to stay abstinent (where abstinence is the preferred and usual lifestyle of the subject), starting at Screening (signing the ICF) and continuing throughout the clinical study period, and for 30 days after IP administration.

e. These requirements do not apply to subjects in a same sex relationship.

6. Female subjects of non-childbearing potential are eligible to participate if 1 of the following conditions apply:
    a. Must have a confirmed clinical history of sterility (documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, as confirmed by review of the subject's medical records, medical examination, or medical history interview)
    b. Must be postmenopausal as defined as: amenorrhea for at least 1 year prior to Screening and a laboratory confirmed serum follicle-stimulating hormone (FSH) level ≥40 mIU/mL. Female subjects on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods (Appendix 3) from Screening (signing the ICF) until at and continuing throughout the clinical study period, and for 30 days after IP administration if they wish to continue their HRT during the study.
7. Female subjects must agree not to donate ova starting at Screening (signing the ICF) and continuing throughout the clinical study period, and for 30 days after IP administration.
8. Subject agrees not to participate in another interventional study while participating in the present clinical study.

5.1.2 Parts A (Single Ascending Dose Study) and B (Multiple Ascending Dose Study)

9. Healthy male and female, non-smoking, subjects between the ages of 18 and 55 years, inclusive, at the time of Screening. In each cohort, at least 2 male subjects and 2 female subjects should be enrolled.
10. Appropriate general health, as determined by an experienced physician based on a medical evaluation including detailed medical history, clinical laboratory tests, vital signs, 12-lead ECG, and full physical examination (and neurological assessment).

5.1.3 Part C (Proof-of-Concept Study)

11. Male and female subjects between the ages of 18 and 75 years (inclusive) who have undergone total or partial pancreatectomy or have an established diagnosis of CP, as confirmed by fecal pancreatic elastase-1 <100 μg/g in formed stools within 12 months of the Screening visit.
12. Subjects with clinically well controlled EPI under the regular use of PERT (remission or adequate improvement of steatorrhea on PERT), as determined by an experienced physician based on a medical evaluation including detailed medical history, clinical laboratory tests, vital signs, 12-lead ECG, and full physical examination (and neurological assessment).
13. 150_{min} percentage $^{13}CO_2$ excretion rate <4.4% dose/h using the Pancreo-Lip breath test at Screening.

5.2 Exclusion Criteria

Subjects are excluded from the study if ANY of the following criteria apply at any time starting from Screening up to Day 1 prior to IP administration:

5.2.1 All subjects

1. Female subject who has been pregnant within the 6 months prior to Screening or breastfeeding within the 3 months prior to Screening.
2. Treatment with any antiplatelet and/or anticoagulant medication, except low-dose aspirin.
3. Evidence or history of specific food intolerance. Examples include gluten intolerance, lactose intolerance, or dairy food intolerance or any food/ingredient included in the standard breakfast provided at the study site.
4. A positive result, on Screening, for serum hepatitis B surface antigen, hepatitis A virus antibodies, hepatitis C virus antibodies or antibodies to human immunodeficiency virus type 1 and/or type 2.
5. Known active infection with COVID-19, or a suspected infection with severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2]).
6. Chronic alcoholic intoxication that would preclude compliance with the study procedures.
7. Habitual use of nicotine products or smoking within 3 months (>10 cigarettes per day) prior to Screening, and/or unwilling to refrain from smoking during the confinement period. Nicotine replacement therapy is allowed during the study.
8. Drug addiction that would preclude participation and compliance with study procedures.
9. Subject has a pulse rate <40 or >100 bpm; mean systolic blood pressure (SBP) >150 mmHg; mean diastolic blood pressure (DBP) >95 mmHg at Screening. Repeat measurements are allowed at the discretion of the Investigator.
10. Subject has any clinically significant abnormalities at Screening in rhythm, conduction or morphology of the resting ECG and any clinically significant abnormalities in the 12-lead ECG, as considered by the Investigator, that may interfere with the interpretation of QTc interval changes including abnormal ST-T wave morphology.
11. Subject has prolonged QTcF >450 msec for male subjects or >470 msec for female subjects or a family history of prolonged QT syndrome, at Screening.
12. Plasma donation within the 14 days prior to the first dose of IP or any whole blood donation/significant blood loss >500 mL during the 3 months prior to the first dose of IP.
13. Treatment with any investigational drug or device/treatment within the 30 days or 5 half-lives of the drug (whichever is longer) prior to the administration of IP.
14. Known allergy or adverse reaction history to any component of the CDX-7108 oral dose formulation.

5.2.2 Part A (Single Ascending Dose Study) and Part B (Multiple Ascending Dose Study)

15. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies and childhood asthma) at time of Screening or IP administration, that in the opinion of the Investigator may put the subject at greater safety risk, influence response to study drug, or interfere with study assessments.
16. Current or chronic history of GI disorders or conditions interfering with normal GI anatomy or function. Examples include GI bypass surgery, partial or total gastrectomy, gastric band surgery, major (>1 m) small bowel resection, vagotomy, malabsorption, Crohn's disease, ulcerative colitis, irritable bowel syndrome, celiac sprue, and small intestinal bacterial overgrowth.
17. A positive Screening test for use of drugs (amphetamines, cocaine, marijuana, opiates, barbiturates, benzodiazepines, methadone, and methamphetamines) and alcohol (breath test). However, there is the option to re-screen once during the Screening period at the discretion of the Investigator or delegate in the case of a positive result at Screening for a prescribed medication, eg, codeine.
18. Subject has any clinically significant abnormalities in hematology, coagulation, clinical chemistry, or urinalysis at Screening as judged by the Investigator, including aspartate aminotransferase (AST) or ALT >1.5 times above the ULN. Repeat measurements are allowed at the discretion of the Investigator.
19. Use of any prescribed or nonprescribed medication in the 2 weeks preceding the first dose of IP. EXCEPTION: Subjects who have received approved vaccines (including approved COVID-19 vaccines) may be allowed if these vaccines are taken no less than 72 hours prior to the IP dose at the discretion of the Investigator.

5.2.3 Part C (Proof-of-Concept Study)

20. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies and childhood asthma) at time of Screening or IP administration, that in the opinion of the Investigator may put the subject at greater safety risk, influence response to study drug, or interfere with study assessments. NOTE: Subjects with treated diabetes secondary to CP or pancreatectomy are allowed.
21. Subject has any clinically significant abnormalities in hematology, coagulation, clinical chemistry, or urinalysis at Screening as judged by the Investigator, including AST or ALT >1.5 times above the ULN, or cholesterol or triglycerides >400 mg/dL. Repeat measurements are allowed at the discretion of the Investigator.
22. Current or chronic history of GI disorders or conditions interfering with normal GI anatomy or motility, with the exception of pancreatic insufficiency due to pancreatectomy or CP.

23. Use of any prescribed or nonprescribed medication potentially interfering with gastric pH, intestinal motility, or fat absorption, including herbal and dietary supplements and antacids; these medications shall be stopped for a minimum of 5 times their half-life before IP administration if, in the opinion of the Investigator, this does not represent a risk for the subject's wellbeing. EXCEPTIONS:
    - Histamine H2 receptor antagonists, PPI, insulin, analgesics, and chronic pain medications.
    - Oral contraceptives, paracetamol, or multivitamins.
    - Subjects who have received approved vaccines (including approved COVID-19 vaccines) may be allowed if these vaccines are taken no less than 72 hours prior to the IP dose at the discretion of the Investigator.
24. Use of antibiotics within 8 days before the Pancreo-Lip breath test at Screening or Day 1.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

1. Subjects are not permitted to consume any foods known to modulate cytochrome P450 enzyme activity (including grapefruit, pomelos, star fruit, Seville oranges, or food products containing these ingredients) within 14 days prior to Day −1 and for the duration of the confinement period.
2. Subjects should refrain from consumption of any foods containing poppy seeds within 24 hours prior to Screening and admission to the study site to avoid false positive drug screen results.
3. Subjects should fast overnight (for at least 10 hours) prior to clinical laboratory tests at Screening. On dosing days, the breakfast meal in Part A and all meals in Part B should be consumed within 20 minutes of the start of the meal. In Part B, meals will be provided at regular intervals of 4 hours.
4. In Part C (POC study), subjects will be required to fast overnight (for at least 10 hours) prior to the Pancreo-Lip breath test. At Screening (Day −35), subjects will receive a standardized meal consisting of a slice of toast with 10 g of butter and 10 g of a chocolate cream (Nutella®, Ferrero, Germany) mixed with ^{13}C-MTG substrate (200 mg glyceryl 1,3-dioctadecanoate 2-octanoate-1-^{13}C in pure powder form), as part of the Pancreo-Lip breath test procedure. The meal can be accompanied with 150 mL of black coffee, tea, or still water. Thereafter, subjects will remain fasted for at least 4 hours following dosing and the meal. Further drinks are not allowed until the end of the breath test, with the exception of a small amount of water (<100 mL). On Day 1 and Day 8, subjects will receive the same standardized meal (breakfast) to be consumed within 10 minutes of the start of the meal.

5.3.2 Alcohol and Tobacco

1. Subjects will abstain from alcohol for 48 hours prior to the first dose of IP administration, during confinement at the study site until discharge, and 24 hours prior to ambulatory visits.

At all other times during the study until completion of the study, subjects are discouraged to consume alcohol, but may consume no more than 2 drinks per day. One drink is equivalent to 12 g alcohol = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of 80-proof distilled spirits.

2. Subjects will be permitted to smoke ≤9 cigarettes or equivalent per day until the EOS visit, but use of tobacco- or nicotine-containing products will not be allowed during confinement at the study site and for 24 hours prior to ambulatory visits. Nicotine-replacement therapy will be permitted. In Part C, subjects are not allowed to smoke directly prior to the Pancreo-Lip breath test as it influences its efficacy.

5.3.3 Activity

1. Subjects should refrain from strenuous exercise within 48 hours prior to admission to the study site up to 7 days following the last IP dose. Subjects may participate in light recreational activities during the study (eg, watching television, reading). Normal physical activity may be resumed beyond these periods. In Part C, subjects are not allowed to exercise exhaustively (high-performance sports/strenuous exercise) directly prior to the Pancreo-Lip breath test as it influences its efficacy.
2. Subjects will be advised not to donate blood or plasma during the study period.

5.4 Screen Failures

All Screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all subjects screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled or randomly assigned to the IP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information including demography, screen failure details, eligibility criteria, and any SAEs should be recorded in the electronic Case Report Form (eCRF) for screen failures.

Individuals who do not meet the criteria for participation in this study (screen failure), but at some point in the future meet all of the subject eligibility criteria, may be rescreened once (only if the Investigator considers the cause of the initial Screening failure to be of an acute and completely reversible nature). If the rescreening occurs outside the 28-day window, all other assessments performed at the initial Screening visit should be repeated during the rescreening visit. Rescreened subjects should not be assigned the same subject number as for the initial Screening.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol.

6.1 Investigational Products Administered

The IP (CDX-7108 bulk drug solution and matching placebo) will be supplied by the Sponsor. Details of the IP are provided in Table 7. Subjects will receive a single oral dose or multiple oral doses of the IP according to a predetermined randomization schedule. The dosage levels for Part A (SAD study), Part B (MAD study), and Part C (POC study) are indicated in Table 8.

Table 7 Study Treatment Details

IP Name	**CDX-7108**	**Placebo**
Dose Formulation	CDX-7108 in *tris*(hydroxymethyl)aminomethane, sodium chloride, sucrose, and water	Excipients only: *tris*(hydroxymethyl)aminomethane, sodium chloride, sucrose, and water
Bulk Drug Dosage Form	Clear to slightly opalescent, and colorless to yellow solution	Clear and colorless solution (Diluent)
Bulk Drug Dose Concentration	30 (±3) mg/mL	0 mg/mL
Route of Administration	Oral	
Dose Preparation	CDX-7108 Oral Dosing Solution: To achieve the required dose strengths for each cohort for oral administration, the Bulk Drug Solution is to be diluted with a Diluent including a flavored syrup to make up a total volume of 30 mL (refer to the Pharmacy Manual for details). The flavored syrup is added to ensure the active and placebo oral dosing solution is identical in taste and appearance.	The Diluent will be added to appropriate amount of flavored syrup to make a total volume of 30 mL and to ensure that the active and placebo oral dosing solution is identical in taste and appearance (refer to the Pharmacy Manual for details).
Dosing Instructions	Trained personnel will facilitate and observe the administration of the IP in a blinded manner. The oral dosing solution should be taken in 3 fractions throughout the meal consumption (10 mL at the start, 10 mL mid-way though, and 10 mL at the end). A small volume of water will be used to rinse the container and will be drunk by the subjects to ensure full dose ingestion. In Part A (SAD study), the IP will be administered orally together with breakfast, which should be consumed within 20 minutes of the start of the meal. In Part B (MAD study), the IP will be administered orally 4 times a day for 6 consecutive days together with meals (breakfast, lunch, afternoon snack and dinner), which should be consumed within 20 minutes of the start of the meal. Meals will be provided at regular intervals (every 4 hours). In Part C (POC study), following an overnight fast of at least 10 hours, the IP will be administered orally together with a standardized breakfast with ^{13}C-MTG substrate (Section 5.3.1), which should be consumed within 10 minutes of the start of the meal. The meal can be accompanied with 150 mL of black coffee, tea, or still water. No food should be allowed for at least 4 hours following dosing and breakfast. Further drinks are not allowed until the end of the breath test, with the exception of a small amount of water (<100 mL).	

Packaging and Labeling	All clinical study material will be packaged and labeled in compliance with GMP and local regulatory requirements and must be provided with a certificate of analysis.
Manufacturer	AGC Biologics GmbH, Czernyring 22, 69115 Heidelberg, Germany

Abbreviations: IP = investigational product; GMP = Good Manufacturing Practices; MAD = multiple ascending dose; MTG = mixed triglyceride; POC = proof-of-concept. SAD = single ascending dose.

Table 8 Anticipated Dose Levels in Each Study Part

Study Part	Cohort/Treatment Group	Anticipated Dose Level
Part A (SAD study)	A1	10 000 lipase units
	A2	50 000 lipase units
	A3	150 000 lipase units
	A4	250 000 lipase units
	A5	500 000 lipase units
Part B (MAD study)	B1	50 000 lipase units
	B2	150 000 lipase units
	B3	250 000 lipase units
Part C (POC study)	CDX-7108	150 000 lipase units

Abbreviations: MAD = multiple ascending dose; POC = proof-of-concept; SAD = single ascending dose.
Note: Dose levels may be adjusted based on emerging data obtained from previous cohorts.

6.2 Handling/Storage/Accountability

1. On receipt of the IP, the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP. The IP storage conditions are described in the Pharmacy Manual.
2. Only subjects enrolled in the study may receive the IP and only authorized study site staff may supply or administer IP.
3. All IP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study site staff. The Sponsor reserves the right to inspect the IP storage area before and during the study. A written record will be made of the storage condition of the study materials and retained for the Investigator File.
4. The Investigator is responsible for IP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records) at the study site. The amount of IP received from the Sponsor, the amount supplied and/or administered to subjects will be documented.
5. The IP will be dispensed by an authorized pharmacist from the site according to predefined drug dispensing requirements. The Investigator, a member of the study site staff, or a hospital pharmacist must maintain an adequate record of the receipt and

distribution of all IP using appropriate IP accountability forms. These forms must be available for inspection at any time.

6. During the study, all used IP containers will be retained until a study monitor has reviewed the IP accountability logs. Unused IP will be returned to the Sponsor or destroyed by the site according to their SOPs on confirmation by the Sponsor. Further guidance and information for the final disposition of used and unused IP are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

Prior to the start of the study, a computer-generated randomization schedule will be created by an unblinded statistician and uploaded into the electronic data capture (EDC) system (Medidata Rave Randomization and Trial Supply Management). For each cohort in Part A (SAD study), randomization to CDX-7108 or placebo will be in a 4:2 ratio (Sentinel 1:1, rest of cohort 3:1). For each cohort in Part B (MAD study) randomization to CDX-7108 or placebo will be in a 4:2 ratio. Provisions will be made to include optional additional cohorts in the randomization scheme. For Part C (POC study) randomization to CDX-7108 or placebo will be in a 1:1 ratio to one of the 2 treatment sequences: CDX-7108→placebo or placebo→CDX-7108.

The following personnel will have access to the randomization list:

- The unblinded study site pharmacist.
- Staff in the central bioanalytical laboratory who are responsible for analyzing the PK samples.
- The safety team to allow expedited reporting of suspected unexpected serious adverse reactions (SUSARs) to local regulatory authorities.

After signing the ICF, each subject will be assigned a Screening number according to the Screening order. Following confirmation of eligibility on Day 1, subjects will be allocated a unique randomization number sequentially based on the predetermined randomization schedule, and according to their chronological order of inclusion in the study. Once a randomization number has been assigned it must not be reassigned. Further details of randomization number allocation are provided in the Pharmacy Manual. Both the Screening and randomization numbers will be used to identify the subject throughout the study period and on all study-related documentation.

If a subject is replaced after randomization but prior to dosing (Section 7.2), the replacement should be allocated the same treatment as the original subject to ensure that the treatment groups remain balanced.

6.3.2 Blinding

This is a double-blind study and therefore, apart from prespecified unblinded individuals, the Investigator, site staff, Sponsor, Sponsor's delegates (if applicable) and subjects will all be blinded to treatment. No individual subject information that can potentially unblind the Investigator or subject will be reported until the end of the study. The presentation of the placebo will be indistinguishable in appearance and taste to CDX-7108 due to the addition of flavored syrup. An unblinded study pharmacist will be used to prepare and dispense the IP.

The Investigator will remain blinded unless knowledge of the subject's treatment assignment is necessary for the clinical management or welfare of the subject. The reason for unblinding will be clearly documented.

After each cohort has completed, the SRC will determine the dose level for the next cohort. This decision will generally be made without unblinding the subject's treatment assignment. If judged necessary by the SRC, an individual or the complete cohort may be unblinded during evaluation of the study data. Before unblinding, a decision should be made about the action to be taken based on the revealed treatment allocation.

During the study period, drug concentration information that may unblind the study will not be reported to study sites or blinded personnel until the study has been unblinded.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor and Sponsor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

Emergency unblinding will be managed through the EDC system (Medidata Rave). The eCRF guidelines and a communication plan will describe the procedure for subject-level unblinding of the study. The randomization form in the EDC system has an 'Unblind' function for Investigator users, which will allow the Investigator to determine what treatment was administered to subject in the case of an emergency.

6.4 Investigational Product Compliance

The prescribed dosage, timing, and mode of IP administration may not be changed, except as defined in Section 6.7. Any departures from the intended regimen must be recorded in the eCRF.

All dose administrations will be performed at the study site under the supervision of appropriately trained staff. A mouth check will be performed following each dose administration

to make sure the dose has been swallowed. The details of IP administration will be recorded in both the source documents and eCRF. Treatment of overdose is described in Section 8.5.

6.5 Measures to Ensure Subject Safety at the Study Site

The clinical staff at the study site are responsible for the ongoing safety and wellbeing of the subjects while they are in the study site. The site is a Phase 1 clinical site that has all the necessary emergency equipment required and has internal SOPs that are to be followed in the event of an untoward medical emergency. There is a paging system to alert the clinical staff to any area in the study site where a subject may need medical attention. In the case of an emergency, cardiac resuscitation trolleys are found in the main ward areas of the study site. These trolleys contain drugs, equipment for airway insertion, circulation lines, defibrillation etc, together with oxygen cylinders with delivery apparatus and portable suction machines. In addition, there will be a physician on site during normal business hours (up to 8 hours postdose on each dosing day) and medical advice is available by phone 24 hours a day. In addition, if necessary the clinical staff can contact further on call physicians or public emergencies services in the event of a serious medical event. Equipment and emergency drugs are available to treat common medical emergencies that might occur in a Phase 1 study.

6.6 Warnings and Precautions

As this is the first administration of CDX-7108 in humans, all effects cannot be reliably predicted. The preclinical data suggest an acceptable safety margin. Facilities and staff for resuscitation and the treatment of other medical emergencies will be provided.

6.7 Prior and Concomitant Medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment (within 30 days before Screening) or receives during the study must be recorded on the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose, unit, form, frequency, and route.

If the use of any concomitant treatment becomes necessary (eg, for treatment of an AE), the treatment and administration details must be recorded in the source documents and the eCRF. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1 Prohibited Medications

In Part A (SAD study) and Part B (MAD study), subjects must abstain from taking any prescribed or nonprescribed medication (including over-the-counter medications, dietary

supplements, and herbal remedies such as St. John's Wort extract) within 14 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of the IP until completion of the EOS/ET visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

In Part C (POC study), subjects must abstain from taking any prescribed or nonprescribed medication potentially interfering with gastric pH, intestinal motility or fat absorption (including herbal and dietary supplements, and antacids) within 5 half-lives of the drug prior to the first dose of the IP until completion of the EOS/ET visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study. See exceptions in Section 6.6.2. Use of antibiotics is also prohibited within 8 days before the Pancreo-Lip breath test at Screening and on Days 1 and 8.

Use of prohibited medications during the study will be captured as protocol deviations and discussed with the Sponsor.

6.6.2 Allowed Medications

Subjects who intend to receive approved vaccines (including approved COVID-19 vaccines) may be allowed during the study if these vaccines are taken no less than 72 hours prior to the IP dose at the discretion of the Investigator.

The following medications are allowed at any time during the study:

- Part C [POC study] only: Histamine H2 receptor antagonists, PPI, insulin, analgesics, and chronic pain medications.
- Paracetamol/acetaminophen, at doses of up to 4 g in 24 hours, but no more than 1 g in 4 hours.
- Ibuprofen at doses <1.2 g in 24 hours.
- Multivitamins or vitamin C at daily recommended doses.
- For female subjects, hormonal contraceptives or HRT.

Other concomitant medication may be considered on a case-by-case basis if the Investigator and Medical Monitor agree that the use is not contradicted.

6.7 Dose Modification

The details of dose selection are described in Section 4.3, dose escalation criteria in Section 4.6, and study stopping criteria in Section 4.7 of this protocol. The proposed dose levels/dosing frequency of CDX-7108 may be adjusted (including de-escalating to a lower dose level or investigating an intermediate dose level) over the course of the study depending on the emerging safety, tolerability, and available serum PK data.

6.8 Treatment After the End of the Study

In this study, no further treatment or medical care is planned or required after the EOS visit.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Investigational Product

Individual subjects must be withdrawn from further IP administration if any of the following occurs:

- Occurrence of AEs not compatible with the continuation of IP administration in the study, in the Investigator's opinion
- COVID-19 or confirmed infection with SARS-CoV-2: If an enrolled subject develops symptoms and signs compatible with SARS-CoV-2 infection, laboratory confirmation of SARS-CoV-2 infection, as determined by local SARS-CoV-2 testing guidelines, should be performed. Any subject who has confirmed SARS-CoV-2 infection may be required to prematurely discontinue study medication following a discussion between the Investigator and Medical Monitor.
- Death
- Withdrawal of consent
- Protocol deviations, including use of prohibited concomitant medication or noncompliance judged as significant by the Investigator and/or the Sponsor
- Loss to follow-up (see Section 7.3)
- Termination of the study by the Investigator or Sponsor
- Inadvertent enrollment: If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject must be discontinued from IP administration and the Sponsor or Sponsor designee must be contacted.

If the IP is prematurely discontinued, the primary reason for discontinuation must be recorded in the appropriate section of the eCRF. Subjects who discontinue the IP must be followed up by the Investigator and undergo the assessments and procedures scheduled for the EOS/ET visit, where possible. Such subjects will not be replaced.

7.2 Subject Discontinuation/Withdrawal from the Study

The study stopping criteria for individual subjects and dose escalation stopping criteria (individual cohorts) due to safety/tolerability concerns in each study part are described in Section 4.7.

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons, including:

- Occurrence of AEs not compatible with the continuation of subject participation in the study, in the Investigator's opinion, or unacceptable to the subject to continue
- Death

- Withdrawal of consent
- Protocol deviations, including use of prohibited concomitant medication or noncompliance judged as significant by the Investigator and/or the Sponsor
- Loss to follow-up (see Section 7.3)
- Investigator request
- Intercurrent illness
- Termination of the study by the Investigator or Sponsor

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study site source documents.

Should a subject request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. See the Schedule of Assessments (Table 1, Table 2, and Table 3) for data to be collected at the time of ET and for any further evaluations that need to be completed. Subjects withdrawing due to an AE should be followed up according to the procedures for the EOS/ET visit.

Termination of the study as a whole is described in Appendix 1.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the study site for a required study visit:

- The study site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 contact attempts and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.4 Subject Replacement

Subjects who voluntarily withdraw from the study and subjects withdrawn due to protocol deviations prior to randomization and IP administration may be replaced following discussion with the Investigator and Sponsor. The decision regarding the replacement of subjects will be

documented. Subjects withdrawn after randomization and IP administration or who are withdrawn due to an AE will not be replaced.

It is anticipated that alternate subjects will be required to ensure 6 subjects are dosed for each cohort. The study site will have alternate subjects admitted and ready for dosing in each cohort of each study part. Therefore, if a subject withdraws after randomization but prior to dosing on Day 1, the subject can be immediately replaced with one of the alternate subjects.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing for each study part are summarized in the Schedule of Assessments (Table 1, Table 2, and Table 3).

Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct. Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the Sponsor immediately on occurrence or awareness to determine if the subject should continue or discontinue the IP.

At visits in Part A (SAD study) and Part B (MAD study) when multiple postdose procedures are required to be conducted at the same nominal time point, the timing of PK blood sample collections will take priority over all other scheduled activities. The following order is recommended: perform vital signs first, followed by ECGs as close as possible to the scheduled time point but prior to PK sampling; perform PK sampling at the scheduled time point; perform other sampling; perform physical examination. All other procedures should be performed as close as possible to the scheduled time point but may be obtained before or after PK sampling.

For Part C (POC study) when multiple postdose procedures are required to be conducted at the same nominal time point, the Pancreo-Lip breath test procedure should be prioritized and the following order is recommended: perform PD assessment (Pancreo-Lip breath test) first followed by vital signs, ECGs, blood sampling, and lastly, physical examination. All other procedures should be performed as close as possible to the scheduled time point but may be obtained before or after PD assessments.

8.1 Demographics and Other Baseline Characteristics

At Screening, the following demographic data will be collected and reported in the eCRF: age at enrollment and year of birth, sex, race, and ethnicity, and female reproductive status (woman of childbearing potential [WOCBP], postmenopausal, or surgically sterile). History of substance use, including tobacco use, alcohol intake, and recreational drug use will be documented in the source documents.

8.2 Efficacy Assessments

Not applicable.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Assessments (Table 1, Table 2, and Table 3).

8.3.1 Medical, Surgical, and Medication History

A complete medical history will include evaluation for any past or present medical conditions, including a review of GI symptomatology, history of all known allergies, and surgical history.

A review of prior medications will be completed as specified in Section 6.6. Prior medications are those used within 30 days of Screening until Day 1 prior to IP administration.

8.3.2 Height, Body Weight, and BMI

Body weight (in kg, at time points specified in Table 1, Table 2, and Table 3) and height (in cm, only at Screening) will be measured to allow the calculation of BMI (rounded to 1 decimal place).

Wherever possible, body weight must be taken using the same weighing scale for each subject at subsequent visits and consistent methods between subjects. In order to get comparable body weight values, body weight measurements should be performed as follows:

- In the fasted state (except for the Screening visit)
- After urine sampling (body weight after bladder voiding)
- Subjects should wear light clothes; shoes and coats/jackets should be taken off; and pockets should be emptied of heavy objects (ie, keys, coins etc).

8.3.3 Vital Signs

Vital signs measurements will include SBP, DBP, pulse rate, respiratory rate and body temperature as outlined in the Schedule of Assessments (Table 1, Table 2, and Table 3).

Systolic blood pressure, DBP, and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in the supine or semi-supine position and in a quiet setting without distractions (eg, television, cell phones) and will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Wherever possible, vital signs measurements must be taken using the same body position at subsequent visits and consistent methods between subjects.

All vital signs measurements will be documented at each visit, and the details will be recorded in both the source documents and the eCRF. The Investigator (or a qualified observer at the investigational site) will also evaluate the overall results using 1 of the following categories: normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS) and record his/her evaluation in the eCRF. Vital signs may be repeated at the discretion of the Investigator to confirm errant readings.

8.3.4 Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the Schedule of Assessments (Table 1, Table 2, and Table 3) after the subject has rested comfortably in the supine or semi-supine

position for at least 5 minutes using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS duration, QT interval, and QTcF interval. Refer to Section 4.7.2 for QTc-related stopping criteria.

For triplicate ECGs, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 1 minute apart. The full set of triplicates should be completed in <4 minutes. Wherever possible, ECG measurements must be taken using the same body position at subsequent visits and consistent methods between subjects.

All ECG data will be documented at each visit, and the details will be recorded in both the source documents and the eCRF. The Investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: normal, abnormal NCS, or abnormal CS and record his/her evaluation in the eCRF. The ECGs may be repeated at the discretion of the Investigator to confirm errant readings.

8.3.5 Physical Examinations

Physical examinations will be performed by a study-delegated registered physician at time points outlined in the Schedule of Assessments (Table 1, Table 2, and Table 3). A complete physical examination will include, at a minimum, assessments of general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, GI system, musculoskeletal system, lymph nodes, and nervous system. A brief symptom-directed physical examination may be performed at all other visits and at any time throughout the study, as clinically indicated.

Any findings made during the physical examination must be noted regardless of if they are part of the subject's medical history. The Investigator (or a qualified observer at the investigational site) will evaluate the findings using 1 of the following categories: normal, abnormal NCS, or abnormal CS and record his/her evaluation in the eCRF. New CS abnormalities that occur after IP administration will be recorded as treatment-emergent AEs (TEAEs).

8.3.6 Safety Laboratory Assessments

Safety clinical laboratory samples will be analyzed at the study site's local laboratory. See Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Assessments for the timing and frequency (Table 1, Table 2, and Table 3).

Venous blood samples will be collected for clinical laboratory evaluations including hematology, coagulation, clinical chemistry, viral serology, serum pregnancy, and FSH testing (when applicable). Blood samples will be collected either by direct venipuncture (any suitable vein) or via an indwelling cannula inserted in a vein (depending on the time point).

Urine will be collected for urinalysis (and urine microscopy, if required), urine pregnancy testing, and urine drugs of abuse screen. A commercially available breathalyzer test will be used to determine the concentration of alcohol in the subject's breath.

The processing, shipping, and analysis of samples for protocol-required laboratory tests will be carried out as per a Laboratory Manual and the study site's SOPs. Repeated or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The laboratory reports must be filed with the source documents. The Investigator must review the laboratory report and document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Refer to Section 8.4.1.3 for details on reporting of laboratory abnormalities as AEs.

8.3.7 Immunogenicity (Anti-CDX-7108 Antibody) Assessments

Venous blood samples for the development of anti-CDX-7108 antibodies in serum will be collected from all subjects as per the Schedule of Assessments timing and frequency (Table 1, Table 2, and Table 3). Blood samples will be collected either by direct venipuncture (any suitable vein) or via an indwelling cannula inserted in a vein (depending on the time point). The actual date and time (24-hour clock time) of each sample, and the reason for any samples not collected, will be recorded in the eCRF.

Instructions for the collection and handling of biological samples, including details for sample collection, labeling, storage, and shipping will be provided in a Laboratory Manual. Repeated or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The immunogenicity assessments will be performed at a central laboratory using a validated immunoassay method. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report. NOTE: These data will be analyzed and reported separately outside the clinical study database.

8.4 Adverse Events

Adverse events will be reported by the subject. The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IP or study procedures, or that caused the subject to discontinue the study (see Section 7.0). Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4.1 Definitions

8.4.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject, temporally associated with the use of an IP, whether or not considered related to the IP. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the IP.

Events meeting the AE definition include:

- Any abnormal laboratory test results (hematology, coagulation, clinical chemistry, or urinalysis) or other safety assessments (eg, vital signs measurements, ECG, or physical examinations), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not associated with the subject's health status).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after IP administration although it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events that do NOT meet the definition of an AE include:

- Medical or surgical procedures (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not represent a clinically significant exacerbation or worsening.

Adverse events which commence or worsen in severity on or after the time of the first dose of IP will be considered as TEAEs.

8.4.1.2 Serious Adverse Events

If an event is not an AE per definitions above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization: In general, hospitalization signifies that the subject has been detained (usually involving a stay of at least 24 hours) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
  - Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect: Intrauterine development of an organ or structure that is abnormal in form, structure, or position.
- Is a medically important event or reaction: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed above. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.4.1.3 Recording of Adverse Events Based on Other Safety Assessments

For protocol-specified laboratory parameters, any laboratory abnormality that is new in onset or which has worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded on the AE pages of the eCRF if not captured as part of an overarching diagnosis (eg, hemoglobin of 8 g/dL captured as part of anemia):

- Requires therapeutic intervention or additional diagnostic tests.
- Has accompanying clinical symptoms or signs.
- Is judged by the Investigator as clinically significant.

Any clinically significant deterioration in vital signs, ECGs, and physical examinations as compared with baseline should also be recorded as AEs.

8.4.2 Recording of Adverse Events

All AEs will be recorded from the time of IP administration (Day 1) until the end of the subject's participation in the study. Any medical occurrences reported after obtaining informed consent but before IP administration will be recorded as medical history. All SAEs will be recorded from the time of Screening (signing the ICF).

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information in the eCRF, including the following details (each event must be recorded separately):

- A description of the event
- Onset and resolution dates and times
- Seriousness
- Severity (as defined in Section 8.4.2.1)
- Relationship to the IP (as defined in Section 8.4.2.2)
- Action taken (action taken with the IP, other actions taken)
- Outcome (Fatal, Not recovered/Not resolved, Recovered/Resolved, Recovered/Resolved with sequelae, Recovering/Resolving, or Unknown)

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

It is **not** acceptable for the Investigator to send photocopies of the subject's medical records in lieu of completion of the AE/SAE page of the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the Medical Monitor and/or Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to Medical Monitor and/or Sponsor.

8.4.2.1 Assessment of Severity

Based on their clinical judgment, the Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Mild:** An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
- **Moderate:** An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- **Severe:** An AE that prevents normal everyday activities; treatment or other intervention usually needed.

Note: the term "severe" does not necessarily equate to "serious". Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.4.2.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be recorded. If an AE changes in frequency or intensity over a number of days, a new entry of the event must be made in the eCRF (with distinct onset dates).

8.4.2.2 Assessment of Causality

The Investigator is obligated to assess the relationship between the IP and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the IP will be considered and investigated. The Investigator will also consult the IB in their assessment.

The causal relationship of the AE to the IP or study procedures should be assessed by the Investigator (or medically qualified delegate) using the following classification (Table 9).

Table 9 Causal Relationship of Adverse Events to the Investigational Product

Category	Description
Related	• The AE follows a reasonable temporal sequence from IP administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, or concomitant medications). o The AE follows a reasonable temporal sequence from IP administration and represents a known reaction to the IP or other drugs in its class or is predicted by the known pharmacological properties of the drug.) o The adverse events resolves with discontinuation of the IP and/or recurs with re-challenge, if applicable.
Not related	• Adverse events do not follow a reasonable temporal sequence from IP administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases and concomitant medications).

Abbreviations: AE = adverse event; IP = investigational product.

8.4.3 Reporting of Serious Adverse Events and Regulatory Reporting Requirements

As the Sponsor has a legal responsibility to notify the appropriate regulatory authorities about the safety of a new test drug, prompt notification by the Investigator or designee of any SAEs to the Sponsor is required.

All SAEs, whether related or unrelated, will be reported electronically through the EDC system (Medidata Rave) and submitted to the Sponsor and/or designee within 24 hours of site awareness. When reporting via the EDC system is not possible (eg, system failure or access

problems), the SAE must be reported by completing a paper SAE Report Form. The Investigator will submit any updated SAE data to the Sponsor and/or designee within 24 hours of it being available. The procedures for completing and transmitting SAE reports and contact information for SAE reporting can be found in the SAE Report Completion Guidelines.

Copies of all correspondence relating to reporting of any SAEs should be maintained in the site's study files and will be checked routinely by the study monitor.

The Sponsor will comply with local regulatory requirements relating to safety reporting to the regulatory authority, Health and Disability Ethics Committee (HDEC)/Human Research Ethics Committee (HREC), and Investigators. If the Sponsor consider that an SAE is a SUSAR, it will be reported to the appropriate regulatory authorities by the Sponsor (or designee) within the predefined timelines. Investigator Alert Letters must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. An Investigator who receives an Investigator Alert Letter describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the HDEC/HREC according to local requirements.

8.4.4 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs/SAEs documented at a previous visit/contact that are designated as ongoing will be followed up until resolution, stabilization, the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 7.3). This activity will continue up to the EOS/ET visit. The Investigator will ensure that follow-up includes any supplemental investigations as medically indicated or requested by the Medical Monitor and/or Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. For nonserious AEs that are reported close to or the EOS/ET visit, follow-up of ongoing events that are considered related to the IP will continue only up to the time of database lock.

A poststudy AE/SAE is defined as any event that occurs outside of the nominal AE/SAE study reporting period. Investigators are not obligated to actively seek AE/SAE in former subjects after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has completed the study and he/she considers the event reasonably related to the IP or study participation, the Investigator will promptly notify the Sponsor.

8.4.5 Pregnancy

There is no information about the effects that CDX-7108 could have on the development of the fetus in humans. Therefore, it is important that female subjects and female partners of male study subjects do not become pregnant during the study and agree to use adequate contraception.

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator. Female subjects who become pregnant during the study will be immediately withdrawn from the IP.

Details of all pregnancies in female subjects and female partners of male subjects (after obtaining the necessary signed informed consent from the pregnant female partner directly) will be collected from the time of IP administration until at least 3 months (90 days) after the last dose of IP.

The Investigator will record pregnancy information electronically through the EDC system (Medidata Rave) (or on a Pregnancy Report Form if the EDC system fails) and submit it to the Sponsor and/or designee within 24 hours of learning of the pregnancy. The procedures for completing and transmitting pregnancy reports and contact information for pregnancy reporting can be found in the Pregnancy Report Completion Guidelines.

The pregnant female subject or female partner of the male subject will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up period for a pregnancy will be deemed to have ended when the health status of the child has been determined on its birth. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, hospitalizations for complications during pregnancy, or if the outcome of the pregnancy meets the criteria of an SAE (eg, spontaneous abortions, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or elective termination of a pregnancy will be reported as an SAE (Section 8.4.3).

8.5 Treatment of Overdose

CDX-7108 doses to be administered in this study are greatly lower than the doses proven to be safe in nonclinical studies. No specific safety issue linked to possible IP overdose is expected. For this study, any dose of CDX-7108 greater than the highest daily dose included in this clinical study within a 24-hour time period will be considered an overdose. However, considering the controls in place for subjects in this study and given that the IP will be administered by trained site staff, it can be assumed that the risk of overdose with CDX-7108 is very low. In the event of an overdose, it is recommended that the occurrence be reported to the Sponsor and Medical

Monitor, and the subject be closely monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

8.6 Pharmacokinetics (Part A and Part B)

8.6.1 Collection of Samples and Determination of CDX-7108 Concentrations

Venous blood samples will be collected for measurement of serum concentrations of CDX-7108 at time points specified in Table 1 and Table 4. Blood samples will be taken either by direct venipuncture (any suitable vein) or an indwelling cannula inserted in a vein (depending on the time point). The actual date and time (24-hour clock time) of each sample, and the reason for any samples not collected, will be recorded in the eCRF.

Instructions for the collection and handling of biological samples, including details for sample collection, labeling, storage, and shipping will be provided in a Laboratory Manual.

Samples for the determination of CDX-7108 concentrations in serum will be analyzed at a central laboratory using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.

8.6.2 Calculation of Derivation of Pharmacokinetic Variables

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 8.3.1 or higher (Certara, LP Princeton, New Jersey, United States [US]) and/or SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, US). Actual elapsed time from dosing will be used for the final serum PK parameter calculations.

Serum Pharmacokinetic Parameters

The PK parameters in Table 10 and Table 11 will be determined for serum CDX-7108, when possible. Additional serum PK parameters may be calculated if deemed appropriate. Drug concentration information that may unblind the study will not be reported to study sites or blinded personnel until the study has been unblinded.

Table 10 Serum Pharmacokinetic Parameters – Part A (SAD study)

Pharmacokinetic Parameter	Definition
C_{max}	Maximum concentration, obtained directly from the observed concentration versus time data.
$AUC_{0\text{-}inf}$	Area under the serum concentration-time curve from time zero extrapolated to infinity, calculated by linear up/log down trapezoidal summation.
$AUC_{0\text{-}t}$	Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation.
T_{max}	Time to C_{max}.
$t_{1/2}$	Terminal elimination half-life.

Abbreviation: SAD = single ascending dose.

Table 11 Serum Pharmacokinetic Parameters – Part B (MAD study)

Pharmacokinetic Parameter	Definition
$C_{ss,max}$	Maximum steady state serum concentration.
C_{τ} (predose)	Predose concentration Day 1 to Day 6.
$AUC_{0-\tau}$	Area under the plasma concentration-time curve over the dosing interval, calculated by linear up/log down trapezoidal summation.
AUC_{0-t}	Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation.
T_{max}	Time to C_{max}.
$t_{1/2}$	Terminal elimination half-life.

Abbreviation: MAD = multiple ascending dose.

8.7 Serum Lipase Activity (Part A and Part B)

In Part A (SAD study) and Part B (MAD study), venous blood samples will be collected for measurement of serum lipase activity at time points specified in Table 1 and Table 4. These samples will be analyzed at the study site's local laboratory.

Blood samples will be taken either by direct venipuncture (any suitable vein) or an indwelling cannula inserted in a vein (depending on the time point). The actual date and time (24-hour clock time) of each sample, including the reason for any samples not collected, will be recorded in the eCRF. Instructions for the collection and handling of biological samples, including details for sample collection, labeling, storage, and shipping will be provided in the Laboratory Manual and the study site's SOPs.

8.8 Pharmacodynamics

8.8.1 Collection of Breath Samples and Determination of Pancreatic Lipase Activity (Part C only)

At Screening, to confirm the subjects' severe EPI status, and on Day 1 and Day 8, to determine rate of lipid absorption of CDX-7108, the Pancreo-Lip breath test will be performed by measuring breath samples from subjects with EPI in Part C (POC study) (Table 3).

The Pancreo-Lip breath test needs at least 10 hours of prior overnight fasting. Subjects are not allowed to smoke or exercise exhaustively directly prior to the Pancreo-Lip breath test as it influences its efficacy.

The test protocol for Pancreo-Lip will take approximately 4 hours and 10 minutes to complete and will be performed as per the manufacturer's instructions.[11,12,13,14] The test is to be carried out with the subject in a resting position. The test is initiated by taking 2 baseline (reference) breath samples. The subject blows gently through a plastic straw into a glass tube which is sealed with a

rubber stopper. Subjects will then consume a standardized meal (Section 5.3.1) containing the ^{13}C-MTG substrate (Screening test) or will receive the IP together with the standardized breakfast (Days 1 and 8), which should be consumed within 10 minutes of the start of the meal. A further 8 breath samples will be taken at 30-minute intervals over 4 hours (240 minutes) post meal (or post dose and meal) as per time points specified in Table 5. The sample tubes will be placed in the original kit pack and sent to INFAI GmBH for $^{13}CO_2$ determination using mass spectrometry. Repeated or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The procedure for breath sample collection, and instructions for processing, and shipping of breath samples will be provided in the Breath Test Procedure Manual.

The following PD parameters will be derived:

- Percentage $^{13}CO_2$ excretion rates over baseline (% dose/h)
- 150_{min} percentage $^{13}CO_2$ excretion rate (% dose/h)
- Percentage $^{13}CO_2$ cumulative excretion (% dose)

8.9 Genetics/Biomarkers

Genetics/biomarkers are not evaluated in this study.

8.10 Health Economics/Medical Resource Utilization

Health economics/medical resource utilization parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Given that this is a Phase 1 FIH study, no formal statistical hypothesis testing will be performed.

9.2 Sample Size Determination

Given the exploratory nature of this study, the sample size is not based on formal statistical considerations but is typical for FIH studies. Any statistical testing will be considered exploratory and descriptive. In the dose escalation studies, a sample size of 6 subjects per cohort, with a total of at least 30 subjects in Part A (SAD study) (5 cohorts) and at least 18 subjects in the Part B (MAD study) (3 cohorts), and a sample size of 10 subjects in Part C (POC study) is expected to be sufficient to meet the objectives of the study.

9.3 Populations for Analyses

For purposes of analysis, the analysis populations in Table 12 are defined.

Table 12 Analysis Populations

Analysis Populations	Description
Screened Population	All subjects who sign the ICF.
Randomized Population	All subjects who are randomized into this study. Subjects will be analyzed according to their randomized treatment, regardless of which treatment the subject actually received. This population will be used for all summaries of baseline and demographic data.
Safety Population	All randomized subjects who receive any amount of the IP. Subjects will be analyzed according to the treatment they actually received, if this differs from that to which the subject is randomized. This population will be used for the summaries of all safety and tolerability data, and serum lipase activity data.
Pharmacokinetic Population	All randomized subjects who receive any amount of CDX-7108 and have at least 1 evaluable serum PK parameter. Subjects will be analyzed according to the treatment they actually receive, if this differs from that to which the subject is randomized. Subjects with dosing deviations that could potentially affect the PK profile will be excluded from the PK Population, at the discretion of the pharmacokineticist.
Pharmacodynamic Population	All randomized subjects in Part C (POC study) who receive any amount of the IP and have at least 1 evaluable PD result (Pancreo-Lip breath test assessment) at baseline and postdose in both the crossover treatment periods. Subjects will be analyzed according to the treatment they actually received, if this differs from that to which the subject is randomized.

Abbreviations: ICF = informed consent form; IP = investigational product; PD = pharmacodynamic; PK = pharmacokinetic; POC = proof of concept.

9.4 Statistical Analyses

The following sections describe the statistical analysis as it is foreseen when the study is being planned. A detailed Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe the subject analysis populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. The SAP will also provide the format of listings, tables, and figures to be provided for completion of the Clinical Study Report (CSR). Any deviations from the SAP will be presented in the final CSR. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All statistical analyses, summaries, and listings will be performed using SAS software (Version 9.4 or higher) (SAS Institute, Inc., Cary, North Carolina, US).

Results in Part A (SAD study), Part B (MAD study), and Part C (POC study) will be analyzed and summarized separately. In Parts A (SAD study) and B (MAD study), data will be presented for each CDX-7108 dose group and for the pooled placebo group. Data for all CDX-7108 dose groups combined and all study subjects combined will also be presented when appropriate. Individual subject data will be presented in listings by cohort and treatment group. In Part C (POC study), data will be presented for each treatment sequence group and by treatment group. Data for all subjects combined will also be presented when appropriate.

The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

- Continuous variables: sample size (n), mean, standard deviation, median, minimum (min), and maximum (max). The coefficient of variation (CV%), geometric mean, and geometric CV% will be presented for PK parameters, where applicable.
- Categorical variables: frequency counts and percentages.

Baseline will be defined as the last available, valid, non-missing assessment (scheduled or unscheduled) prior to dosing. Since Part C (POC study) has a crossover design, 2 baseline values will be considered:

- Baseline 1 will be defined as the last available, valid, non-missing assessment (scheduled or unscheduled) prior to Treatment 1.
- Baseline 2 will be defined as the last available, valid, non-missing assessment (scheduled or unscheduled) prior to Treatment 2.

Only data from protocol-scheduled visits/time points will be included in the summary tables. Data from unscheduled visits/time points will not be included in the summary tables (except for markedly abnormal results), but will be included in the figures and listings.

9.4.1 Subject Disposition and Protocol Deviations

All subjects who provide informed consent (ie, the Screened Population) will be accounted for in this study. Subject enrollment and disposition will be summarized by treatment group (and by treatment sequence group, where applicable) and for all subjects, and will include: the number of subjects entered, screen failed along with reasons for screen failure, enrolled, randomized, and dosed with the IP; the total number of subjects who complete the study; and the number of subjects who discontinue from the study, along with the reason for discontinuation.

The number and percentage (%) of subjects included in each analysis population will also be presented.

Subjects in the Randomized Population with protocol deviations and deviation will be listed and summarized by deviation category, severity classification, by treatment group (and by treatment sequence group, where applicable), and for all subjects using frequency counts and percentages. If applicable, subjects whose study participation is impacted by the global pandemic COVID-19 will be flagged in the protocol deviation listing, with details of the impact.

9.4.2 Demographics, Other Baseline Characteristics, and Medical History

All demographic and baseline data recorded prior to dosing will be summarized using descriptive statistics or frequency counts and percentages, as appropriate, by treatment group (and by treatment sequence group, where applicable) and for all subjects in the Randomized Population. Individual subject demographics and baseline characteristics (including results from urine drug abuse screening, alcohol breath test, viral serology, pregnancy tests, FSH tests, and in Part C (POC study), Pancreo-Lip breath test screening results) will also be presented in listings.

Medical history will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and the data will be listed and summarized using frequency counts and percentages by system organ class (SOC) and preferred term (PT) by treatment group (and by treatment sequence group, where applicable) and for all subjects in the Safety Population.

9.4.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the latest version of the World Health Organization Drug Global Dictionary. Prior medications are those medications that are stopped prior to the first dose of IP. Concomitant medications are medications that are taken at least once after the first dose of IP. Medications stopping on the same day as the first IP administration will be considered as concomitant medications.

Prior and concomitant medications will be listed and summarized separately using frequency counts and percentages by Anatomical Therapeutic Chemical system (Level 2) and drug PT by

treatment group (and by treatment sequence group, where applicable) and for all subjects in the Randomized Population.

9.4.4 Efficacy Analyses

Not applicable.

9.4.5 Safety Analyses

9.4.5.1 Adverse Events

All safety analyses will be performed on the Safety Population. Adverse events will be coded using the latest version of MedDRA.

All AE summaries will be restricted to TEAEs only (as defined in Section 8.4.1.1). An overview summary of the frequency and percentage of subjects with TEAEs, as well as number of TEAEs, overall and by TEAE category will be presented by treatment group based on the time of onset of the TEAE and for all subjects. Treatment-emergent AEs will also be grouped by SOC and PT and summarized by treatment group and for all subjects. In Part C (POC study), TEAEs occurring during the washout period between treatments will be attributed to the last treatment received.

For the summaries of TEAEs, subjects who experience the same TEAE (in terms of the MedDRA SOC and PT) more than once will only be counted once for that event in the number of subjects, but all occurrences of the same event will be counted in the number of events.

Separate summaries will be provided for TEAEs by maximum severity (Mild, Moderate, or Severe) and related TEAEs. Any TEAEs with a missing or unknown severity will be considered as severe in the summary tables.

Treatment-emergent AEs leading to IP discontinuation (for Part B [MAD study] only), TEAEs leading to discontinuation from the study, SAEs, and TEAEs leading to death will be summarized and/or listed separately.

9.4.5.2 Clinical Laboratory Evaluations

Observed values and change from baseline for clinical laboratory data (hematology, coagulation, and clinical chemistry) will be listed and summarized using descriptive statistics at each protocol-specified time point by treatment group. Separate listings will be produced for all parameters for subjects with at least one out-of-range or abnormal clinical laboratory result.

Shifts in hematology, coagulation, and clinical chemistry parameters by reference range categories (low, normal, high) and shifts in the Investigator's evaluation of urinalysis parameters, (Normal, Abnormal NCS, Abnormal CS) from baseline to each postbaseline protocol-scheduled time point will be summarized by treatment group, using frequency tabulations.

9.4.5.3 Vital Signs, Electrocardiograms, and Physical Examinations

All vital signs and ECG results will be presented in data listings. Investigator's evaluation for vital signs, ECGs, and abnormal physical examination findings will be presented in data listings.

In addition, observed values and change from baseline for vital signs and ECG data will be summarized at each protocol-specified time point, by treatment group. Shifts in the Investigator's evaluation of the results (Normal, Abnormal NCS, Abnormal CS) from baseline to each postbaseline protocol-scheduled time point will also be summarized by treatment group using frequency tabulations.

9.4.6 Pharmacokinetic Analyses (Part A and Part B)

Serum CDX-7108 concentrations will be listed for all subjects in the Safety Population. Summaries of serum CDX-7108 concentrations and derived PK parameters will be based on the PK Population.

Serum CDX-7108 concentrations will be listed and summarized using descriptive statistics by treatment group and nominal PK sampling time point. All serum CDX-7108 concentrations that are below the limit of quantification will be labeled as such in the concentration data listings. Individual and arithmetic mean (per treatment) serum concentration-time profiles will also be presented graphically.

Pharmacokinetic parameters of serum CDX-7108 will be listed and summarized by treatment group using descriptive statistics. A regression power model, relating log-transformed C_{max} and AUC parameters to log-transformed dose, will be used to investigate dose proportionality following single-dose and multiple dose administration. Individual and geometric mean C_{max} and AUC parameters will be plotted graphically against dose level. Predose concentrations on Days 1 to 6 will be summarized for Part B (MAD study). Further details will be provided in the SAP.

9.4.7 Analysis of Serum Lipase Activity (Part A and Part B)

Serum lipase activity values will be listed and summaries of serum lipase activity will be based on all subjects in the Safety Population.

Observed values of mean serum lipase activity (%) will be summarized using descriptive statistics at each protocol-scheduled time point and by treatment group. The mean values of serum lipase activity will also be plotted over time by treatment group.

An exploratory exposure-response analysis may be undertaken to characterize the relationship between CDX-7108 concentrations and serum lipase activity.

9.4.8 Pharmacodynamic Analyses (Pancreatic Lipase Activity) (Part C only)

The PD parameters will be listed for all subjects in the Safety Population. Descriptive summaries of the PD parameters will be presented per scheduled-protocol time point and based on the PD Population. The mean values of PD parameters will also be plotted over time for each treatment.

9.4.9 Handling of Missing Data

For subjects who are withdrawn from the study prior to their completion for any reason, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal. Subjects who are withdrawn prematurely from IP will be included in all analyses regardless of the duration of treatment. There will be no imputation for missing data, unless otherwise stated.

9.5 Interim Analyses

No interim analyses are planned for this study.

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11.0 APPENDICES

Appendix 1 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - New Zealand Medicines and Medical Devices Safety Authority regulations.
  - Australian Therapeutic Goods Administration regulations.
  - All other applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an HDEC/HREC by the Investigator and reviewed and approved by the HDEC/HREC before the study is initiated.
- The Investigator or designee will be responsible for the following:
  - Providing written summaries of the status of the study to the HDEC/HREC annually or more frequently in accordance with the requirements, policies, and procedures established by the HDEC/HREC.
  - Notifying the HDEC/HREC of SAEs or other significant safety findings as required by HDEC/HREC procedures.
  - Providing oversight of the conduct of the study at the study site and adherence to requirements of ICH guidelines, the HDCE/HREC, and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 5). The study will not start at a study site at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study site.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Finance and Insurance

Financing of this study is outlined in a separate agreement.

Subjects may be compensated for the time that they spend participating in the study using a formula determined by the study site.

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files. The subject should not take part in any other clinical study while they are enrolled in this study. The subject should report any health injury that could have occurred as a result of the clinical study to the Investigator without delay.

Informed Consent Process

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to ICH GCP guidelines. The Investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before the subject has given written informed consent to participate in the study.

The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study. Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH GCP guidelines, the HDEC/HREC, and study site.

The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign and date the ICF. A copy of the ICF(s) must be provided to the subject. Representative written information for the subject (subject information sheet) and a sample ICF, designated as the master version, is provided in the Trial Master File.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the HDEC/HREC (and regulatory authorities, if required). Subjects must be reconsented to the new version of the ICF.

Subjects who are rescreened are required to sign a new ICF.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate HDEC/HREC members, and by inspectors from regulatory authorities.

Administrative Structure

The Sponsor will enlist the support of a contract research organization (CRO), IQVIA™, to coordinate the study. The Sponsor will supervise all outsourced activities. The administrative structure for the study will be covered in a separate document.

An SRC will be established for this study; the details are provided in Section 4.5.

Medical Monitor

Ashish Soman, MD
Medical Director
IQVIA
Mobile: +61 (0)412 834 448

Dissemination of Clinical Study Data

After completion of the study, a CSR will be written by the CRO in consultation with the Sponsor and Investigator following the guidance in ICH E3. The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the regulatory authority and the HDEC/HREC a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

- All subject data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). Data collection must be completed for each subject who signs an ICF.
- The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF. The Investigator must also maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, HDEC/HREC review, and regulatory agency inspections and provide direct access to source data documents.
- The CRO is responsible for the data management of this study, including quality checking of the data.

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. Where permitted, remote monitoring (and remote source data verification) may occur to facilitate ongoing data review if an on-site visit is not able to be performed due to SARS-CoV-2 related events.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Management of Protocol Amendments and Protocol Deviations

Protocol Amendments:

No changes (amendments) to the protocol may be implemented without prior approval from the Sponsor and the appropriate HDEC/HREC, except where necessary to eliminate an immediate hazard to subjects, or when the change involves only logistical or administrative aspects of the study. If a protocol amendment requires changes to the ICF, the revised ICF must be approved by the HDEC/HREC.

Protocol Deviations:

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes that were approved by the Sponsor and the HDEC/HREC and agreed to by the Investigator. Protocol deviations will be classified by severity ratings of major or minor, as determined by clinical staff:

- A minor protocol deviation is any change, divergence, or departure from the study design or procedures of the study protocol, and which does not have a major impact on the subject's rights, safety or wellbeing, or the completeness, accuracy, and reliability of the study data.
- A major protocol deviation is a deviation that has an impact on subject safety, can substantially alter risks to subjects, have an effect on the integrity of the study data, or affect the subject's willingness to participate in the study.

Major deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to a regulatory agency's regulations or ICH GCP guidelines, and may lead to the subject being withdrawn from the study or being excluded from statistical analyses.

The Investigator or designee will document and explain in the subject's source documentation any deviation from the approved protocol. Protocol deviations will also be documented by the study monitor throughout the course of monitoring visits, and the Investigator will be notified of any deviations in writing by the monitor. The HDEC/HREC will be notified of all protocol deviations, if appropriate, in a timely manner.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. The Investigator may only implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior HDEC/HREC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments will be submitted to the HDEC/HREC (and regulatory authorities if applicable) for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

Study Termination and Study Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed on study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the Investigator or designee will promptly inform the HDEC/HREC and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant study termination or suspension or early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- The Investigator (or delegate) and the Sponsor consider that the number and/or severity of AEs justify discontinuation of the study.

- Failure of the Investigator to comply with the protocol, the requirements of the HDEC/HREC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further IP development.
- The Sponsor makes a unilateral request to do so.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study site will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 2 Clinical Laboratory Tests

The tests detailed in Table 13 will be performed locally as per the time points specified in the Schedule of Assessments (Table 1, Table 2, and Table 3). Protocol-specific laboratory-related requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.

Subjects will be required to fast overnight (for at least 10 hours) before clinical laboratory sample collection at Screening (in all study parts) and on dosing days (in Part C [POC study] only).

Investigators must document their review of each laboratory safety report. Laboratory/analyte results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations or the local laboratory SOPs.

Table 13 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Red blood cell (erythrocyte) count	Mean cell hemoglobin concentration
	Platelet (thrombocyte) count	White Blood Cell (Leukocyte) Count with Differential:
	Hemoglobin	Neutrophils
	Hematocrit	Lymphocytes
	Red Blood Cell Indices:	Monocytes
	Mean corpuscular volume	Eosinophils
	Mean corpuscular hemoglobin	Basophils
	Reticulocyte count	
Coagulation	INR	Activated partial thromboplastin time
	Prothrombin time	Fibrinogen
Clinical Chemistry[a]	Bicarbonate	Creatine kinase
	Albumin	Uric acid/Urate
	Total Protein	AST
	Blood glucose (fasting at Screening only)	ALT
	Sodium	ALP
	Potassium	GGT
	Phosphate	Total bilirubin
	Calcium	Triglycerides
	Urea	Total cholesterol
	Creatinine	Lactate dehydrogenase
	Chloride	C-reactive protein

Laboratory Assessments	Parameters	
Urinalysis	Leucocyte esterase	Blood
	Protein	pH
	Urobilinogen	Nitrite
	Ketones	Specific gravity
	Bilirubin	Urobilinogen
	Microscopy	Glucose
Viral serology (Screening only)	HIV 1 and 2 antibodies	HBsAg
	HAV antibody	HCV antibody
Urine Drugs of abuse (Screening and Day −1, Parts A and B only)	Amphetamines	Benzodiazepines
	Cocaine	Methadone
	Marijuana	Barbiturates
	Opioids and Opiates	Phencyclidine
Alcohol testing	Alcohol breath test using a commercial breathalyzer (Screening and Day -1 only)	
Pregnancy and FSH tests	Serum β-hCG (at Screening) and urine hCG (at Day −1 and EOS) pregnancy tests will be performed for women of childbearing potential only. An FSH test will be performed at Screening (to confirm postmenopausal state).	
Serum Lipase Activity	Part C only	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; anti-HBc = hepatitis B core antibody; COVID-19 = coronavirus disease 2019; eGFR = estimated glomerular filtration rate; EOS = end of study; FSH = follicle-stimulating hormone; GGT = gamma glutamyl transferase; HAV = hepatitis A virus; HbA1c = glycated hemoglobin; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Notes:

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 4.7.2 and Appendix 4. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) (or ALT ≥3 × ULN and INR >1.5) may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.

Appendix 3 Contraceptive Guidance

- When having penile-vaginal intercourse with a WOCBP who is not currently pregnant, nonsterilized male subjects are required to use a male condom and have their partner use 1 of the highly effective contraceptive methods from Screening (signing the ICF) until at least 90 days after the last dose of IP administration, as described in the table below.
- Female subjects of childbearing potential are eligible to participate if they agree to follow 1 of the following highly effective methods of contraception, from Screening (signing the ICF) until at least 30 days after the last dose of IP administration, as described in the table below.

Highly Effective Female Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable. • Implant (that releases progesterone into the bloodstream).
Highly Effective Female Contraceptive Methods That Are User Independent [a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device. • Intrauterine hormone-releasing system.
Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the IP, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized starting at Screening and throughout the study period up to 3 months (90 days) after the last dose of IP.

Appendix 4 Liver Safety: Suggested Actions and Follow-up Assessments

Phase 1 liver chemistry stopping criteria are designed to assure subject safety and to evaluate liver event etiology.

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td colspan="2">

If ALT or AST ≥3×ULN AND bilirubin ≥2 × ULN (>35% direct bilirubin) (or ALT ≥3 × ULN and INR >1.5), report as an SAE [a, b]
ALT ≥5 × ULN
ALT ≥3 × ULN, if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity (such as fatigue, nausea, vomiting, pain, or tenderness in the right upper quadrant, fever, rash, or eosinophilia)

See additional actions and follow-up assessments below.
</td></tr>
<tr><th colspan="2">Required Actions and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td>

Immediately discontinue the IP
Report the event within 24 hours
Complete the liver event page on the eCRF, and complete an SAE report if the event also met the criteria for an SAE [b]
Perform liver function follow-up assessments
Monitor the subject until LFT abnormalities resolve, stabilize, or return to baseline (see MONITORING)

MONITORING:
If ALT ≥3 × ULN AND bilirubin ≥2 × ULN or INR >1.5

Repeat LFTs (include ALT, AST, ALP, bilirubin, and INR) and perform liver function follow-up assessments within 24 hours.
Monitor subject twice weekly until LFT abnormalities resolve, stabilize, or return to baseline.
A specialist or hepatology consultation is recommended.

</td><td>

Obtain INR and recheck with each liver chemistry assessment until the transaminase values show downward trend
Obtain blood sample for PK analysis after the most recent dose [c]
Serum CPK and LDH
Fractionate bilirubin, if total bilirubin ≥2 × ULN
Complete blood count with differential to assess eosinophilia
Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF
Record use of concomitant medications (including acetaminophen, herbal remedies, and other OTC medications) on the concomitant medications eCRF
Record alcohol use on the liver event alcohol intake eCRF

</td></tr>
</table>

Actions	Follow-Up Assessments
If ALT ≥3 × ULN AND bilirubin <2 × ULN and INR ≤1.5: • Repeat LFTs (include ALT, AST, ALP, bilirubin, and INR) and perform liver function follow-up assessments within **24 to 72 hours** • Monitor subject's weekly until liver function abnormalities resolve, stabilize, or return to baseline	**If ALT ≥3 × ULN AND bilirubin ≥2 × ULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins • Serum acetaminophen-adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week) [15] • Liver imaging (ultrasound, MRI, or CT) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRFs

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; CT = computerized tomography; eCRF = electronic Case Report Form; HPLC = high-performance liquid chromatography; IgG = immunoglobulin G; INR = international normalized ratio; IP = investigational product; LDH = lactate dehydrogenase; LFT = liver function test; MRI = magnetic resonance imaging; OTC = over-the-counter; PK = pharmacokinetic; SAE = serious adverse event; ULN = upper limit of normal.

a. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue IP if ALT ≥3 × ULN **and** bilirubin ≥2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

b. All events of ALT or AST ≥3 × ULN AND bilirubin ≥2 × ULN (>35% direct bilirubin) (or ALT ≥3 × ULN and INR >1.5) indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE**.

c. Record the date/time of the PK blood sample draw and the date/time of the last dose of IP prior to the PK blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Laboratory Manual.

Appendix 5 Signature of Investigator

PROTOCOL TITLE: A 3-part, Phase 1a/1b, first-in-human, randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, and pharmacokinetics of single and multiple ascending doses of oral CDX-7108 in healthy adult subjects and to evaluate proof-of-concept via pharmacodynamics of a single dose of oral CDX-7108 in subjects with exocrine pancreatic insufficiency.

PROTOCOL NO: 2102CLI

VERSION: 1.0 (Original Protocol)

DATE: 28 May 2021

This protocol is a confidential communication of Nestlé Health Science, Société des Produits Nestlé, Switzerland. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study site in which the study will be conducted. Return the signed copy to Sponsor and CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Study Site: _____

_____

_____

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Certificate Of Completion

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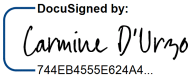
Alexander Smith asmith@aimmune.com Alexander Smith Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 6AA44009-903B-4DF7-8179-CF9B73CAF16D Using IP Address: 157.131.113.113 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 6/1/2021 4:08:26 AM Viewed: 6/1/2021 8:48:55 AM Signed: 6/1/2021 8:49:25 AM
Electronic Record and Signature Disclosure: Accepted: 6/1/2020 11:16:54 AM ID: edfda671-fa3a-45c3-b232-ee2267c4f809		
Carmine D'Urzo Carmine.DUrzo@nestle.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 744EB455-5E62-4A4A-A372-8E5CE31047D8 Using IP Address: 165.225.94.89 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 6/1/2021 4:08:26 AM Viewed: 6/1/2021 5:13:23 AM Signed: 6/1/2021 5:15:05 AM
Electronic Record and Signature Disclosure: Accepted: 6/1/2021 5:13:23 AM ID: e810502d-28d2-4d9b-bc61-d5e18fedd119		

Signer Events	Signature	Timestamp
Edward J. Edson eedson@aimmune.com Associate Director, Clinical Operations Aimmune Therapeutics Security Level: Email, Account Authentication (Required)	Edward J. Edson Signature Adoption: Pre-selected Style Signature ID: 768DF445-0730-4675-9DB7-6F08EB24CD63 Using IP Address: 90.204.74.19 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 6/1/2021 4:08:27 AM Viewed: 6/1/2021 4:43:46 AM Signed: 6/1/2021 4:45:08 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Maximilian Eynatten maximilian.eynatten@nestle.com Security Level: Email, Account Authentication (Required)	DocuSigned by:  BB390267972B486... Signature Adoption: Drawn on Device Signature ID: BB390267-972B-4862-BA7C-E1DD62097482 Using IP Address: 165.225.94.88 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 6/1/2021 4:08:27 AM Viewed: 6/1/2021 4:37:34 AM Signed: 6/1/2021 4:38:20 AM
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In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	6/1/2021 4:08:27 AM
Certified Delivered	Security Checked	6/1/2021 4:37:34 AM
Signing Complete	Security Checked	6/1/2021 4:38:20 AM
Completed	Security Checked	6/1/2021 8:49:25 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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ii. send us an email to agawande@aimmune.com and in the body of such request you must state your email, full name, mailing address, and telephone number. Consent cannot be withdrawn once the documents are signed off.. Consent cannot be withdrawn once the documents are signed off..

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