Official Title: A Phase IIa, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamic Effects of GDC-6599 in Patients with Chronic Cough

NCT Number: NCT05660850

Document Date: Protocol Amendment Version 4: 03-May-2024

PROTOCOL

TITLE:	**A PHASE IIa, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMIC EFFECTS OF GDC-6599 IN PATIENTS WITH CHRONIC COUGH**
PROTOCOL NUMBER:	GA43590
VERSION NUMBER:	4
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 154293 EU CT Number: Not applicable
TEST PRODUCT:	GDC-6599 (RO7441345)
SPONSOR NAME AND ADDRESS:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
4	See electronic date stamp on final page.			
3	13 April 2023			
2	17 September 2022	United Kingdom	1	22 June 2023
1	2 March 2022			

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol GA43590 has been amended to reduce patient burden, add clarity on study conduct, and to incorporate changes made to the United Kingdom-specific version of the protocol. Protocol GA43590 Version 4 represents a merging of the global protocol (previously Version 3) and region-specific Version 1 (United Kingdom), and includes changes specific to this Version 4 amendment. The changes, along with a rationale for each change, are summarized below.

Changes specific to protocol GA43590 Version 4 are as follows:

- Background information on GDC-6955 has been updated with the most recent clinical data (Sections 1.2, 1.3 and 5.1) to align with the now completed Phase Ia/b study (GA43010).
- Sections 2, 4.5, and Appendices 1 and 2 have been updated to remove the mannitol challenge test from Study Visits 2 and 5 and to make this test optional for Study Visits 4 and 7 to reduce participants' burden. In accordance with this change, the study objectives (Sections 2 [Table 1], 3.3.1, and 3.3.5) have been modified to indicate that the evaluation of treatment effect of GDC-6599 on cough hypersensitivity, as measured by mannitol induced cough-dose ratio, and airway hyperresponsiveness, as measured by mannitol induced PD15 and response-dose ratio, are now exploratory rather than secondary objectives. In making the mannitol challenge test optional, requirements for [redacted] (Sections 3.3.4, 3.3.5, and 4.5.5, and 4.5.10; Appendix 1, footnote l, and [redacted]). Section 4.5.9, Sputum Collection and Processing, has been removed, new Section 4.5.14, Optional Mannitol Challenge Tests, has been added, and subsequent sections renumbered.
- In Sections 3.1.1, 4.1, and 6.1, the total study recruitment has been revised to enroll approximately 30 patients with chronic refractory cough (CRC) with asthma with or without atopy, approximately 30 patients with unexplained chronic cough (UCC) in Cohort A (formerly 20 each), and approximately 20 patients with CRC from chronic obstructive pulmonary disease (COPD) with or without chronic bronchitis (CB) in Cohort B. This change is made because of study objective reprioritization.
- In Section 3.1.1, the requirement to repeat the mannitol challenge test has been removed during re-screening within 6 weeks of initial screening if the patients have screen failed for any reason other than the mannitol challenge test.

- In Section 4.1, eligibility criteria have been amended to better define the patient population and to be consistent with the American College of Chest Physicians/European Respiratory Society (ERS) guidelines on CRC diagnosis:
  - The requirement treatment for asthma, COPD, gastroesophageal reflux disease (GERD) and/or UCC has been reduced from 1 year to a minimum of 12 weeks while maintaining the requirement of a CRC diagnosis for at least 1 year (Section 4.1.1.1). Section 4.4.1, Permitted Therapy, has been updated to align with this change.
  - The requirement for male contraception has been removed (see the updated GDC-6599 Investigator's Brochure dated May 2024) (Section 4.1.1.1).
  - For patients with asthma (Section 4.1.1.2), the duration of both diagnosis and stable background therapy have been reduced from 12 months to a minimum of 12 weeks.
- The language regarding single-patient emergency and non-emergency unblinding requested by the investigator has been updated to align with internal procedures (Section 4.2.2).
- Text has been modified to align with updates to the Roche Global Policy on Continued Access to Investigational Medicinal Products (Section 4.3.5).
- In Sections 4.4.2 and 4.4.4 treatment with xanthines (e.g., theophylline, oxtriphylline) is now prohibited within 24 hours prior to mannitol challenge tests to be consistent with the testing manual.
- In Section 4.5.6, [redacted]
- In Section 4.5.7 and Appendix 1, language has been updated to be consistent with the American Thoracic Society (ATS)/ERS guidelines for spirometry defining “usability” criteria, which allow the use of spirometry measurements where curves do not meet the acceptability/reproducibility criteria but represent the patient’s best efforts. The Investigator may discuss these data with the Medical Monitor as applicable. Accordingly, the repeatability criterion for pre-bronchodilator spirometry (Appendix 1, footnote s) now defines the maximum difference between two largest acceptable forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) measurements as 0.15 L (150 mL) (Appendix 1).
- In Appendices 1 and 2, the following modifications have been made to improve flexibility for sites, reduce patient burden, and clarify timing of assessments:
  - The window from screening to randomization has been expanded from 14 to 21 days and must last a minimum of 7 days. To reduce participant burden, screening visits may occur during a single visit day or over a maximum of 3 days. Clarification has been added to indicate that the VitaloJAK® cough monitoring should start at least 30 minutes after the mannitol challenge tests if performed during a single screening visit (Appendix 1 footnote a).

- The window from the end of washout to second treatment period has been expanded from 3 to 7 days and a clarification has been added to accordingly shift subsequent visit days to ensure 14 days of study treatment for the second treatment period (Appendix 1, Table and footnotes f).
- During the screening period, urine samples are now specified to be collected before mannitol challenge testing. The timing of pharmacokinetic and biomarker samples has been updated in line with aforementioned modifications ([redacted]).

Protocol GA43590 Version 1 (United Kingdom) was generated to address feedback from the Medicines and Healthcare products Regulatory Agency. The following changes specific to Version 1 (United Kingdom), which were implemented at sites in the United Kingdom only, will now be implemented at all sites:

- The inclusion criterion pertaining to body mass index (BMI) has been amended to remove an allowance for BMI values outside the specified range if considered not clinically significant by the investigator (Section 4.1.1.1).
- For consistency with the study design, the inclusion criterion pertaining to chest X-ray or computed tomography scan for all patients has been updated to clarify that this criterion does not apply to COPD, for patients with CRC COPD with or without chronic bronchitis (Section 4.1.1.1).
- The exclusion criterion prohibiting clinical laboratory values outside the reference range for the test laboratory at screening (Study Visit 1) unless the value is deemed not clinically significant by the investigator, with Medical Monitor informed, has been removed (Section 4.1.2).
- Patients with hypomagnesemia will not be excluded from the study. As such, for clarity the examples "hypokalemia, hypomagnesemia, hypocalcemia" have been removed from the exclusion criterion pertaining to history of ventricular dysrhythmias or risk factors for ventricular dysrhythmias (Section 4.1.2).

Protocol GA43590 Version 3 was amended primarily to clarify details of the study design. The following changes specific to the Version 3 protocol, which were not previously implemented at sites in the United Kingdom, will now be implemented at those sites:

- In Section 2 (Table 1) and Section 4.5.5, to clarify the exploratory endpoint of change in mannitol-induced airway hyperresponsiveness (AHR), AHR has been defined as follows: AHR is expressed as response-dose ratio (calculated as maximum percent decrease in FEV_1 [relative to baseline of mannitol challenge] after the last dose of mannitol divided by cumulative dose of mannitol, and PD15 (defined as provoking dose of mannitol that induces a 15% decrease in FEV_1). In this table, change in FEV_1 from baseline to Day 14 has been added as an exploratory endpoint to better evaluate the efficacy of GDC-6599, as compared with placebo, across each chronic cough disease subgroup. To support the new exploratory endpoint, the timing of spirometry has been clarified and an assessment of pre-bronchodilator spirometry has been added on Day 29 (Appendix 1, footnote s).

- In Section 3.1, Appendix 1, and [redacted] the washout periods in the schedule of activities have been updated to a minimum of 14 days (Days 15−28) to allow for cough and inflammation to return to baseline prior to initiating the second treatment period, including the 24-hr objective cough count−assessment at the pretreatment visit (Day 29), to provide a baseline prior to initiating treatment on Day 30. This change aligns with the original intent of the protocol. Subsequent timepoints have been adjusted accordingly.
- In Sections 3.1.1 and 4.5.5 and in Appendix 1 mention of the recording of acute coughs induced during the mannitol challenge using the VitaloJAK system has been removed as manual cough counts during the mannitol challenge cannot be validated in this manner. Details on cough counting during the mannitol challenge are provided in the mannitol challenge test guidance document.
- In Sections 3.1.2 and 6.8, clarification has been provided regarding the structure, roles, and responsibilities of the Internal Monitoring Committee.
- In Figure 1 the coughs-per-dose ratio (CDR) inclusion criterion in the Study Schema has been amended for consistency with the CDR-related inclusion criterion in Section 4.1.1.
- In Sections 4.1.1 and 4.1.2, eligibility criteria have been amended to better define the patient population and reflect the underlying patient population that may eventually benefit from the investigational drug as follows:
  - The inclusion criterion requiring stable background therapy for primary chronic lung disease or gastroesophageal reflux disease has been removed as it was duplicative of the exclusion criterion related to initiation of proton-pump inhibitor therapy within 8 weeks of screening.
  - An inclusion criterion related to smoking history has been added for patients with UCC.
  - The definition of smoking has been clarified as use of inhaled tobacco or cannabis products (e.g., cigarettes, cigars, electronic cigarettes, vaporizing devices, or pipes).
  - The exclusion criterion pertaining to use of oral or systemic corticosteroids has been revised to prohibit these medications for the treatment of respiratory diseases, including cough, within 8 weeks prior to screening. It has been clarified that continued, chronic use of oral or systemic corticosteroids for non-respiratory conditions is permitted, provided patient has been receiving a stable treatment regimen for at least 8 weeks prior to screening and is likely to remain on the stable treatment regimen through completion of the study.
  - The exclusion criteria around respiratory infection (including upper respiratory infection), known coronavirus disease 2019 (COVID-19) infection, persistent symptoms of known prior COVID-19 infection, and/or known positive COVID-19 test have been consolidated; these conditions may not be present within 8 weeks prior to screening.
  - The exclusion criterion of blood transfusion within 8 weeks of screening has been removed.

  - History of recurrent pneumonia has been removed as an exclusion criterion.
  - The exclusionary timeframe around treatment with angiotensin-converting enzyme inhibitor has been reduced from 12 to 8 weeks prior to screening.
  - The exclusion criterion pertaining to treatment with opioids (including codeine), pregabalin, gabapentin, amitriptyline, and nortriptyline has been revised to indicate that treatment with these medications for indications other than chronic cough is permitted, provided patients are receiving a stable treatment regimen for at least 2 weeks prior to screening and, in the opinion of the investigator, are likely to remain on the stable treatment regimen through completion of the study.
  - A criterion excluding treatment with dextromethorphan, guaifenesin, benzonatate, and any other over-the-counter or prescription medication containing an anti-tussive or expectorant for the treatment of cough within 2 weeks prior to screening has been added for consistency with prohibited therapy in Section 4.4.2.
- Sections 4.1.1.2, 4.5.10, and Appendix 1 have been updated to provide operational flexibility such that patients with asthma who do not have confirmed atopic versus non-atopic status in their medical records may undergo either the ImmunoCAP™ Specific IgE test, skin prick test, or radioallergosorbent test for determination of atopic status at screening.
- In Sections 4.1.2, 4.4.1, and 4.4.2, the use of oral or systemic corticosteroids for the treatment of respiratory diseases, including cough, within 8 weeks prior to screening through completion of the end of the second treatment period has been added to prohibited therapy and aligned with the applicable exclusion criterion. Oral corticosteroids as rescue therapy for the treatment of acute exacerbations has been added as permitted therapy during the study.
- In Sections 4.1.2, 4.4.2, and Appendix 12, treatment with medications that are well known to prolong the QT interval within 1 month prior to screening through completion of the study at Visit 8 has been added to prohibited therapy and aligned with the applicable exclusion criterion. A reference list of drugs associated with QT prolongation has been appended to the protocol.
- In Section 4.3.2, details on GDC-6599 dosage, administration, and compliance have been added for clarity.
- In Sections 4.4.1 and 4.4.2 the timeframe for prohibition of the use of opioids (including codeine), pregabalin, gabapentin, amitriptyline, or nortriptyline for the treatment of cough has been modified to last through the end of the second treatment period. In addition, language has been added regarding permitted treatment with these medications for indications other than chronic cough for consistency with language added to the associated exclusion criterion.
- In Section 4.4.2, details regarding treatment with cough-suppressant medication, use of proton-pump inhibitor therapy, and [redacted] have been added to prohibited therapy for alignment with associated exclusion criteria.

- In Section 4.5.5 and Appendix 1, the criteria for discontinuing mannitol doses during the mannitol challenge test have been clarified.
- In Section 4.5.10 and Appendix 1, the IgE f24 (shrimp) test screens for food allergies are no longer required for determining atopic status. As such, these screens have been replaced at screening with the ImmunoCAP Specific IgE test panel, which will be limited to specific IgE against standard allergens including cat dander, dog dander, cockroach, dust mite, mold, and relevant local allergens. To provide operational flexibility, the ImmunoCAP Specific IgE test may be analyzed at the study site's local laboratory or at a central laboratory.
- In Section 5.1.2.1, language has been corrected to indicate that bronchial challenge testing with mannitol should not be performed in any patient with very low baseline pulmonary function tests (e.g., $FEV_1 < 1-1.5$ liters or $< 60\%$ of the predicted values) for consistency with the mannitol challenge guidance.
- In Section 8.4, a description of the technical and organizational security measures taken to protect personal data has been added (Section 8.4).
- In Section 9.5, text has been modified to clarify that summaries of clinical study results may be available for public access in health authority databases.
- In Appendix 1, given that patients are to visit the clinic at Study Visit 3 and Study Visit 6 solely for the purpose of blood chemistry testing (i.e., no pharmacokinetic sample collection at those timepoints), language has been modified to indicate that in-clinic dosing is not required at every clinic visit; patients may self-administer study drug at home on these days.
- In Appendix 1, to clarify timing of VitaloJAK cough recording performed after the optional mannitol challenge test during the treatment periods, the end of the mannitol challenge test has been defined as immediately after spirometry after the last dose of mannitol, or after the final spirometry following the recovery period (if required).
- In Appendix 1, the timing of (patient) administration of the Visual Analog Scale and Numeric Response Scale questionnaires has been clarified.
- In Section 4.5.13, Appendix 1, and [redacted] language has been revised to clarify that the blood sample collection for whole genome sequencing (WGS) or whole exome sequencing (WES) is not applicable for a site that has not been granted approval for WGS/WES, and if the sample is not collected at the specified timepoint, it may be collected at any future timepoint during the study.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IIa, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMIC EFFECTS OF GDC-6599 IN PATIENTS WITH CHRONIC COUGH**
PROTOCOL NUMBER:	GA43590
VERSION NUMBER:	4
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 154293 EU CT Number: Not applicable
TEST PRODUCT:	GDC-6599 (RO7441345)
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the contract research organization.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IIa, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMIC EFFECTS OF GDC-6599 IN PATIENTS WITH CHRONIC COUGH**
PROTOCOL NUMBER:	GA43590
VERSION NUMBER:	4
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 154293 EU CT Number: Not applicable
TEST PRODUCT:	GDC-6599 (RO7441345)
PHASE:	Phase IIa
INDICATION:	Chronic cough
SPONSOR:	Genentech, Inc.

OBJECTIVES AND ENDPOINTS

This Phase IIa, multicenter, randomized, double-blind, placebo-controlled, crossover study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamic (PD) effects of GDC-6599 compared with placebo in patients with a history of chronic cough.

Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of GDC-6599, as compared with placebo, in patients with CRC with asthma or UCC	• Change in cough frequency per hour, assessed objectively over 24 hours (24-hour OCC) using VitaloJAK® cough recorder, from baseline to Day 14
Secondary Objective	**Corresponding Endpoints**
• To evaluate the efficacy of GDC-6599, as compared with placebo, in patients with CRC with asthma or UCC	• Change in the severity of cough, as assessed through the use of the patient-reported cough severity VAS and NRS scores, from baseline to Day 14

24-hour OCC = objective cough count over 24 hours; CRC = chronic refractory cough; NRS = Numeric Response Scale; UCC = unexplained chronic cough; VAS = visual analog scale.

OVERALL DESIGN AND STUDY POPULATION

This Phase IIa, multicenter, randomized, double-blind, placebo-controlled, crossover study is designed to evaluate the efficacy, safety, pharmacokinetics, and PD effects of GDC-6599 across *three* cohorts in patients with chronic cough. In the main study (Part A), approximately 60 patients with chronic cough will be enrolled across *two* cohorts: chronic refractory cough (CRC) with asthma *with or without atopy* (n=*approximately 30*), and unexplained chronic cough (UCC) (n=*approximately 30*). In the substudy (Part B), an additional 20 patients with a diagnosis of CRC with chronic obstructive pulmonary disease (CRC COPD) *with or without chronic bronchitis (CB) (n= approximately 20)* will be enrolled.

Several key aspects of the study design and study population are summarized below.

Phase:	*IIa*	***Population Type:***	*Adult patients*
Control Method:	*Placebo*	***Population Diagnosis or Condition:***	*Chronic cough*
Interventional Model:	*Crossover*	***Population Age:***	*18–80 years, For patients with COPD: ≥ 40 years old*
Test Compounds:	*GDC-6599 (RO7441345) Mannitol (Aridol®/Osmohale®)*	***Site Distribution:***	*Multi-site and multi-region*
Active Comparator:	*Not applicable*	***Study Intervention Assignment Method:***	*Randomized*
Number of Arms:	*Two*	***Number of Participants to Be Enrolled:***	*Approximately 80*

STUDY TREATMENT

During Treatment Period 1, patients will receive [redacted] GDC-6599 or placebo [redacted] for 14 days. Following a 14-day washout period, patients will cross over to the second study period (Treatment Period 2, Study Visits 5–7) and will receive the alternate treatment ([redacted] mg GDC-6599 or placebo) [redacted] for 14 days starting at Study Visit 5.

DURATION OF PARTICIPATION

The study will consist of a screening period of approximately *21* days, followed by a 14-day treatment period. After a 14-day washout, patients will begin another 14-day treatment period during which time the opposite treatment will be administered. A 14-day washout period and [redacted] safety follow-up period will follow. *The total duration of study participation for each patient is expected to be approximately 12–13 weeks.*

COMMITTEES

Independent Committees:	*Not applicable*
Other Committees:	*Internal Monitoring Committee*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[redacted]	
AITC	allyl isothiocyanate
AHR	airway hyperresponsiveness
ATS	American Thoracic Society
AUC	area under the concentration–time curve
AUC_{INF}	area under the concentration–time curve from Time 0 to infinity
[redacted]	
BMI	body mass index
BP	blood pressure
CB	chronic bronchitis
CDR	coughs-per-dose ratio
CE	Conformité Européenne
CHEST	American College of Chest Physicians
CHS	cough hypersensitivity syndrome
C_{max}	maximum concentration observed
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRC	chronic refractory cough
CT	computed tomography (scan)
C_{trough}	trough concentration
DAIDS	Division of AIDS
DBF	dermal blood flow
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
ERS	European Respiratory Society
FDA	(U.S.) Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GERD	gastroesophageal reflux disease
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative

Abbreviation	Definition
GOLD	Global Initiative for Chronic Obstructive Lung Disease
[redacted]	
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
ICS	inhaled corticosteroid
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
LABA	long-acting β-agonist
[redacted]	
LLN	lower limit of normal
MAD	multiple ascending dose
MN	mobile nursing
NGS	next-generation sequencing
NRS	Numeric Response Scale
OCC	objective cough count
PD	pharmacodynamic
PK	pharmacokinetic
PPI	proton-pump inhibitor
PRO	patient-reported outcome
QD	once a day
QTc	corrected QT (interval)
QTcF	QT interval corrected through use of Fridericia's formula
RAST	*radioallergosorbent test*
RBR	Research Biosample Repository
RDR	response-dose ratio
SABA	short-acting β-agonist
SAD	single ascending dose
SMC	Safety Monitoring Committee
t_{max}	time to maximum concentration
TRP	transient receptor potential
TRPA1	TRP ankyrin 1

Abbreviation	Definition
TRPV1	TRP subfamily V, member 1
UCC	unexplained chronic cough
ULN	upper limit of normal
VAS	Visual Analog Scale
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON CHRONIC COUGH

Chronic cough is common, affecting at least 10% of the global population (Song et al. 2015) and representing significant physical and psychosocial burden. Chronic cough is defined as daily cough lasting for more than 8 weeks. Chronic cough, despite investigation and standard-of-care medical management in patients, is termed chronic refractory cough (CRC). CRC is secondary to chronic diseases such as asthma or chronic obstructive pulmonary disease (COPD), whereas unexplained chronic cough (UCC) does not have an identified underlying cause.

Asthma patients specify cough as a bothersome symptom and key aspect of disease burden (Polley et al. 2008; Globe et al. 2015; Gater et al. 2016) and is among the symptoms most frequently reported to clinicians with prominence from the patient perspective (Revicki et al. 1998; Osman et al. 2001; Irwin et al. 2006). Cough is frequently a neglected symptom in uncontrolled asthma and is a major contributor to poor asthma control (Mincheva et al. 2014; Çolak et al. 2019). The burden of cough is reflected in clinical guidelines citing perceived symptoms as a component of severity classification, and symptom reduction a goal of disease management (National Heart, Lung, and Blood Institute 2007; GINA 2016). Cough that persists despite guideline-based treatment in the background of asthma has been referred to as both refractory chronic cough and CRC in consensus guidelines and literature. Within this protocol, chronic cough secondary to asthma will be referred to as CRC.

Cough is also a cardinal symptom of COPD, most frequently reported by patients along with dyspnea and breathlessness, and it is a fundamental component of symptom burden (van der Molen et al. 2003; Arne et al. 2007; Jones et al. 2009; Miravitlles et al. 2014). In patients with COPD, symptom burden, rather than pulmonary function, is more strongly associated with poor health-related quality of life (HRQoL) and more predictive of other negative outcomes such as acute exacerbations (Mahler 1992; Hajiro 1999; van der Molen 2013), as reflected in Global Initiative for Chronic Obstructive Lung Disease (GOLD) clinical staging and management guidelines (Vestbo et al. 2013; GOLD 2019). Cough is a commonly reported symptom of COPD, with 60% to 80% of patients reporting having had a cough within the past 7 days (Kessler et al. 2011; de Oliveira et al. 2013). Cough and mucus disrupt COPD patients' lives at a functional, emotional, social, and economic level (Cook et al. 2019).

Despite the high unmet need, there are currently no approved drugs for the treatment of CRC with asthma, CRC with COPD, or UCC.

The chronic cough that persists in patients with both asthma and COPD, despite standard of care, is postulated to be a consequence of airway afferent nerves activated by bronchial hyperresponsiveness, inflammation, and mucus. Both peripheral and central neural pathways contribute to the regulation of cough and understanding which

of these is active or altered in patients with chronic cough is limited (Mazzone and Undem 2016). In all cases, cough is typically triggered by airway nerves sending impulses to the CNS, often in response to allergens, changes in ambient temperature, air pollution, and chemicals (Satia et al. 2017).

Irrespective of the causes, patients with chronic cough suffer from irritating bouts of coughing evoked by low-levels of thermal, mechanical, or chemical exposure, suggesting an abnormal dysregulation of the cough reflex. Cough hypersensitivity syndrome (CHS) has been proposed to describe this condition. Because activation of peripheral sensory nerves is usually the initiating factor that drives cough, the afferent limb of the cough reflex represents an attractive target for the development of antitussive agents.

Transient receptor potential (TRP) cation channels are localized to airway primary afferents. TRP ankyrin 1 (TRPA1) is a sensory neuronal calcium channel that contributes to airway smooth muscle contraction, sensory neuron hypersensitivity, and neurogenic inflammation, which may lead to bronchoconstriction, airway smooth muscle hyperresponsiveness (AHR), and symptoms like cough in asthma. Genetic deletion or pharmacologic modulation of TRPA1 has been shown to diminish allergen-induced inflammatory leukocyte infiltration, cytokine levels, and AHR in animal models of asthma (Reese et al. 2020; Balestrini et al. 2021). Cough hypersensitivity to agonists of TRPA1 and TRP subfamily V, member 1 (TRPV1) has been demonstrated in patients with a history of UCC (Long et al. 2019). Several TRPV1-specific inhibitors have shown promise to address chronic cough based upon inhibiting cough hypersensitivity to inhaled capsaicin (TRPV1-specific agonist) in CRC/UCC patients, however the results did not translate to any significant benefit in reducing cough frequency (Khalid S et al. 2014; Belvisi MG et al. 2017). [redacted] Development of TRPA1-specific inhibitors and identification of prognostic markers of TRPA1 airway activity may support personalized management of patients with chronic cough and reduce the burden of cough in patients with uncontrolled asthma or COPD.

1.2 BACKGROUND ON GDC-6599

GDC-6599 is a small molecule inhibitor of the TRPA1 channel that is under development as a potential oral therapy for the treatment of patients with CRC with asthma or UCC.

[redacted]

[redacted]

GDC-6599, administered orally (PO), was well tolerated in both rats and cynomolgus monkeys at doses up to 50 mg/kg/day for 4 weeks. The most significant GDC-6599–related finding was a dose-dependent, reversible prolongation of the coagulation parameters aPTT and PT in both rats and monkeys.

[redacted]

GDC-6599 *has been investigated in a completed* Phase Ia/b single ascending dose (SAD) and multiple ascending dose (MAD) study (GA43010) in approximately *81 healthy volunteers* to explore safety, and the pharmacokinetic and pharmacodynamic profile of the agent. Pharmacodynamic target (TRPA1) inhibition *has been evaluated* using the AITC dermal challenge model (Joseph et al. 2021). No significant clinical, laboratory, or ECG findings have been observed in the initial *six dosing cohorts* of the SAD portion and three cohorts of the MAD portion of Study GA43010. Based upon the available clinical data, the clinical dose for the current Phase IIa protocol (GA43590) is [redacted] ([redacted]; see Section 3.3.2). No prior clinical experience with GDC-6599 exists in patients.

Refer to the GDC-6599 Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This Phase IIa cough profiling study will be conducted to evaluate potential inhibition of cough by GDC-6599, a small molecule inhibitor of TRPA1, and its effects on mannitol-induced cough and airway hypersensitivity in a subset of patients with CRC with asthma or UCC. The effects of GDC-6599 on cough and airway inflammation will also be assessed in a subgroup of patients with CRC who have a history of COPD.

The rationale for targeting TRPA1 for the treatment of chronic cough, asthma, and COPD is driven by the potential role of TRPA1 in contributing to airway smooth muscle contraction, sensory hypersensitivity, and neurogenic inflammation, which may lead to bronchoconstriction, AHR, and symptoms such as cough. Anticipated beneficial effects of targeting TRPA1 with GDC-6599 include reduction in bronchoconstriction and cough hypersensitivity in asthma and COPD and a reduction of cough hypersensitivity-associated CRC with asthma or UCC.

GDC-6599 *has been tested* in healthy volunteers in *a completed* Phase Ia/b SAD/MAD Study GA43010. No prior clinical experience with GDC-6599 exists in patients. The rationale for conducting the current study in patients with chronic cough is to evaluate the efficacy, safety, pharmacokinetics, and organ-specific pharmacodynamics (target inhibition in lung) in a relevant patient population.

An assessment has been conducted to determine whether the coronavirus disease 2019 (COVID-19) pandemic has any impact on the benefit-risk assessment of this study including, but not limited to, the patient population under study and study treatment. Review of the summary safety data generated in the initial *six dosing cohorts* of the SAD portion and three cohorts of the MAD portion of the Phase Ia/b SAD/MAD study GA43010 of the potent TRPA1-inhibitor GDC-6599 suggests that inhibition of the TRPA1 receptor is not associated with a higher frequency of infections or clinically significant findings in hematology parameters. Combined with further review of the toxicology data and the mechanism of action of GDC-6599, no impact is anticipated. The safety monitoring and management guidelines and risk mitigation measures provided in the study are considered adequate.

2. OBJECTIVES AND ENDPOINTS

This Phase IIa, multicenter, randomized, double-blind, placebo-controlled, crossover study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamic (PD) effects of GDC-6599 compared with placebo in patients with a history of chronic cough. It will assess the potential benefit of GDC-6599 to reduce cough frequency and severity in patients with a diagnosis of CRC with asthma, UCC, or CRC with COPD. The study will also *explore the eff*ects of GDC-6599 on mannitol-induced cough and/or AHR and the value of mannitol-induced cough hypersensitivity and/or AHR as a prognostic tool in patients with CRC with asthma, UCC, or CRC with COPD as a measure of TRPA1 airway activity. Specific objectives and corresponding endpoints for the study are outlined in Table 1 below.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of GDC-6599, as compared with placebo, in patients with CRC with asthma or UCC	• Change in cough frequency per hour, assessed objectively over 24 hours (24-hour OCC) using VitaloJAK® cough recorder, from baseline to Day 14
Secondary Objective	**Corresponding Endpoints**
• To evaluate the efficacy of GDC-6599, as compared with placebo, in patients with CRC with asthma or UCC	• Change in the severity of cough, as assessed through the use of the patient-reported cough severity VAS and NRS scores, from baseline to Day 14
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of GDC-6599 compared with placebo	• Incidence and severity of adverse events, with severity determined according to the DAIDS toxicity grading scale [a] • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize the PK profile of GDC-6599	• Plasma concentration of GDC-6599 at specified timepoints
Exploratory Objectives	**Corresponding Endpoints**
• *To evaluate mannitol-induced cough response as a measure of TRPA1 airway activity and treatment benefit of GDC-6599, as compared with placebo, in patients with CRC with asthma or UCC*	• *Change in cough hypersensitivity to mannitol, measured as the CDR to mannitol, from baseline to Day 14*

24-hour OCC = objective cough count over 24 hours; AHR = airway hyperresponsiveness*, expressed as RDR (*calculated as maximum percent decrease in FEV_1 *[relative to baseline of mannitol challenge]* after the last dose of mannitol divided by cumulative dose of mannitol*, and PD15 (defined as provoking dose of mannitol that induces a 15% decrease in FEV_1)*; CDR = coughs-per-dose ratio, calculated as total number of provoked coughs divided by cumulative dose of mannitol and expressed as coughs per 100 mg of mannitol; CRC = chronic refractory cough; DAIDS = Division of AIDS; FEV_1 = forced expiratory volume in 1 second; NRS = Numeric Response Scale; PK = pharmacokinetic; RDR = response-dose ratio; UCC = unexplained chronic cough; TRP = transient receptor potential; TRPA1 = TRP ankyrin 1; VAS = visual analog scale.

[a] Adverse events will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (HSS 2017), with slight modifications for clarity and for alignment with internal practices (see Section 5.3.3 and Appendix 10).

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives (cont.)	Corresponding Endpoints (cont.)
• *To evaluate mannitol-induced airway smooth muscle hyper-responsiveness as a measure of TRPA1 airway activity and treatment benefit of GDC-6599, compared with placebo, in patients with CRC with asthma or UCC*	• *Change in mannitol-induced AHR from baseline to Day 14*
• To evaluate the efficacy of GDC-6599, as compared with placebo, across each chronic cough disease subgroup	• Change in 24-hour OCC collected using the VitaloJAK cough recorder from baseline to Day 14 • [redacted] • *Change in FEV_1 from baseline to Day 14* • [redacted] • Change in the severity of cough, as assessed through the use of the patient-reported cough severity VAS score, from baseline to Day 14 • Change in the severity of cough, as assessed through the use of the patient-reported cough severity NRS score, from baseline to Day 14 • [redacted]
• To evaluate cough hypersensitivity and AHR to mannitol across chronic cough disease subgroups	• CDR to mannitol across patients with different background diseases • AHR to mannitol across patients with different background diseases
• [redacted]	• [redacted] • [redacted]

24-hour OCC = objective cough count over 24 hours; AHR = airway hyperresponsiveness, *expressed as RDR (*calculated as maximum percent decrease in FEV_1 *[relative to baseline of mannitol challenge]* after the last dose of mannitol divided by cumulative dose of mannitol*, and PD15 (defined as provoking dose of mannitol that induces a 15% decrease in FEV_1)*; CDR = coughs-per-dose ratio, calculated as total number of provoked coughs divided by cumulative dose of mannitol and expressed as coughs per 100 mg of mannitol; COPD = chronic obstructive pulmonary disease; CRC = chronic refractory cough; FEV_1 = forced expiratory volume in 1 second; [redacted]; NRS = Numeric Response Scale; RDR = response-dose ratio; TRP = transient receptor potential; TRPA1 = TRP ankyrin 1; UCC = unexplained chronic cough; VAS = visual analog scale.

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives (cont.)	Corresponding Endpoints (cont.)
• [redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
• [redacted]	• [redacted]
• To identify and/or evaluate biomarkers that are predictive of response to GDC-6599 (i.e., predictive biomarkers), are early surrogates of efficacy of GDC-6599 treatment, and can provide evidence of GDC-6599 activity (i.e., PD biomarkers, pathway inhibition) as compared with placebo,	• Levels of biomarkers [redacted] at baseline and Day 1 through Day 14
• To evaluate potential relationships between drug exposure and the activity, efficacy, and safety of GDC-6599	• Plasma concentration and PK parameters • PD biomarker endpoints • Efficacy/activity endpoints • Safety endpoints

24-hour OCC=objective cough count over 24 hours; AHR=airway hyperresponsiveness, *expressed as RDR (*calculated as maximum percent decrease in FEV_1 *[relative to baseline of mannitol challenge]* after the last dose of mannitol divided by cumulative dose of mannitol*, and PD15 (defined as provoking dose of mannitol that induces a 15% decrease in FEV_1)*; CDR=coughs-per-dose ratio, calculated as total number of provoked coughs divided by cumulative dose of mannitol and expressed as coughs per 100 mg of mannitol; COPD=chronic obstructive pulmonary disease; CRC= chronic refractory cough; FEV_1=forced expiratory volume in 1 second; [redacted] PD=pharmacodynamic; PK=pharmacokinetic; RDR=response-dose ratio; UCC=unexplained chronic cough; VAS=visual analog scale.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study (Part A and Part B)

This Phase IIa, multicenter, randomized, double-blind, placebo-controlled, crossover study is designed to evaluate the efficacy, safety, pharmacokinetics, and PD effects of GDC-6599 across *three* cohorts in patients with chronic cough. In the main study (Part A), approximately 60 patients with chronic cough will be enrolled across *two* cohorts: CRC with asthma *with or without atopy* (n=*approximately 30*), and UCC

(n=*approximately 30*). In the substudy (Part B), *approximately* an additional 20 patients with a diagnosis of CRC with COPD *with or without chronic bronchitis* (CRC COPD±CB) despite standard-of-care treatment *will be enrolled*.

The study will consist of a screening period of approximately *21* days, followed by a 14-day treatment period. After a 14-day washout, patients will begin another 14-day treatment period during which time the opposite treatment will be administered. A 14-day washout period and [redacted] safety follow-up period will follow.

Patients who meet all eligibility criteria (see Section 4.1) will be randomized in a 1:1 ratio to receive [redacted] mg GDC-6599 or placebo [redacted] for 14 days during the first study period (Treatment Period 1, Study Visits 2–4). Following a 14-day washout period, patients will cross over to the second study period (Treatment Period 2, Study Visits 5–7) and will receive the alternate treatment ([redacted] mg GDC-6599 or placebo) [redacted] for 14 days starting at Study Visit 5.

VitaloJAK® cough recorder (Vitalograph Inc., Maids Moreton, U.K.) will be used to monitor spontaneous cough frequency *at screening and* throughout the study. [redacted]

To characterize the pharmacokinetic (PK) properties of GDC-6599, blood samples will be taken at various timepoints before and after dosing.

To characterize the PD effects of GDC-6599, [redacted] *[collected under prior versions of this protocol]*) will be collected at timepoints indicated in [redacted]

A safety follow-up assessment (Study Visit 8) will be scheduled [redacted] after the last dose of study treatment to ensure patient safety.

At applicable sites, certain study assessments may be performed by a trained nursing professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in mobile nursing (MN) visits and mobile nursing is available.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Patients who are not able to complete the assessments or are unable to meet eligibility requirements during the screening period (screen failure) will be permitted to be re-screened once (for a total of two screenings per patient) at the investigator's discretion. Patients who re-screen ≤6 weeks after Informed Consent Form completion must repeat the assessments that triggered the screen failure. Patients who re-screen >6 weeks after Informed Consent Form completion are required to repeat the consent process and all assessments. The investigator will maintain a record of reasons for screen failure (see Section 4.5.1).

3.1.2 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor patient safety throughout the study. Members from the IMC will *be unblinded to treatment assignment and* include representatives from clinical science, *clinical* safety, *and* biostatistics from the Sponsor. *The IMC may invite representatives from other functional areas (e.g., clinical pharmacology) or external experts on an ad hoc basis when additional expertise is required.* Further details regarding roles and responsibilities will be outlined in the IMC Charter.

Periodic safety reviews of cumulative data will be performed by the Sponsor's IMC as outlined in the IMC Charter. Ad hoc meetings may be held at the request of the IMC or Sponsor at any time to address potential safety concerns. The data to be reviewed will include*, but will not be limited to,* demographics, concomitant medications, study drug administration, adverse events, serious adverse events, adverse events of special interest, ECGs, and relevant laboratory *results*.

At the time of each review, the IMC *may* make recommendations *such as the following*: the trial continues as planned, the trial is stopped for safety reasons, the dose *level or frequency is changed*, additional analyses need to be performed, or enrollment will be held pending further safety evaluations. *The IMC may also provide recommendations on amending the protocol.* Decisions will be made in consideration of the totality of the available data. Final decisions will rest with the Sponsor's study team.

A detailed description of the procedures, data flow, and meeting schedule of the IMC will be provided in the IMC Charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. Each patient is expected to remain in the study for a maximum of approximately 12 weeks. The end of the study is expected to occur approximately 12 weeks after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 18 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

Three cohorts of chronic cough patients with different disease backgrounds (CRC asthma *with or without atopy*, UCC, or CRC COPD) will be enrolled in this study to assess the potential heterogeneity of *treatment effects on cough frequency across disease backgrounds. The study will also explore potential heterogeneity of baseline* cough hypersensitivity to inhaled mannitol and the relationship with *baseline* cough frequency.

Cough is an important symptom of chronic lung disorders and is often cited by patients with CRC with asthma, CRC with COPD, or idiopathic pulmonary fibrosis as the most bothersome of respiratory symptoms having an adverse impact on HRQoL (Polley et al. 2008) and is a key aspect of disease burden and control (Marsden et al. 2016). Despite the high unmet need, there are currently no approved drugs for the treatment of CRC with asthma, UCC, or CRC with COPD.

Chronic cough, despite adherence to guideline-based standard-of-care treatment, represents high unmet medical need in patients with CRC with asthma, UCC, or CRC with COPD. Cough hypersensitivity to inhaled irritants is a key feature of chronic cough. This study will target patients with CRC with atopic asthma, CRC with non-atopic asthma, UCC, and CRC COPD. Patients must have a diagnosis of chronic cough based upon consensus guidelines (American College of Chest Physicians [CHEST] 2018;

European Respiratory Society [ERS] 2020). A mannitol CDR of at least 12 coughs/100 mg is required for inclusion in this study (see Section 4.1.1) in order to identify patients with cough hypersensitivity and avoid including patients with very low mannitol-evoked cough responses, in whom a treatment effect would be difficult to demonstrate.

Heightened and exaggerated cough responses to tussive stimuli is recognized as a unifying feature of patients with chronic cough (Hilton et al. 2013; Canning et al. 2014). However, in the clinical setting, it is clear that the processes regulating cough are heterogeneous across different patient subgroups. Disease-specific profiles of neuronal sensitivity have been demonstrated in the cough responses to inhaled tussive stimuli in patients with COPD, healthy smokers, CRC, asthma, compared with healthy volunteers (Belvisi et al. 2016). The extent to which this may be a consequence of increased activation of vagal afferents by pathology in the airways (e.g., inflammatory mediators, excessive mucus) or an altered neuronal phenotype is unknown. There is recent evidence illustrating distinct patterns of neuronal dysfunction within subsets of UCC patients. A recent study has identified four phenotypes of cough hypersensitivity in patients with UCC based upon activation of the TRPA1 and TRPV1 channels using selective agonists (Long et al. 2019). Data from two recent studies assessing cough hypersensitivity to capsaicin, a TRPV1-specific irritant, in asthma patients suggest that heightened sensitivity to inhaled capsaicin in non-atopic asthma patients relative to atopic patients reflects greater neuronal dysfunction associated with poor asthma control and worse outcomes. (Satia et al. 2017; Kanemitsu et al. 2020). This supports the existence of heterogeneity in cough pathways and an approach for developing personalized anti-tussive therapies.

Understanding the basis for this heterogeneity is key to the development of personalized treatments for cough. This study is designed to profile cough hypersensitivity to inhaled mannitol and the relationship to cough frequency and cough severity across *four distinct subsets* of patients with chronic cough (CRC with atopic asthma, CRC with non-atopic asthma, UCC, and CRC COPD). Treatment with GDC-6599 and placebo across two treatment periods will inform the relative contribution of TRPA1 airway activity to the cough profiles.

3.3.2 Rationale for GDC-6599 Dose and Schedule

The selected dose of GDC-6599 is [redacted]. Based on PK/PD results from the [redacted] of the Phase Ia/b Study GA43010, this dose is expected to [redacted]

At the [redacted] dose of GDC-6599, [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.3.3 Rationale for Control Group

The placebo-controlled crossover design of this study removes patient variation by allowing the patient to serve as their own control. As a result of the inherent variability in cough and other symptoms, the use of a placebo period is necessary to assess safety and efficacy signals that may be attributable to GDC-6599. Patients will not be at increased risk during the placebo period as they will be on standard background therapy for their primary disease and will have access to rescue medication. The addition of a washout period between the two treatment periods is incorporated to prevent the carryover effect of the study drug.

3.3.4 Rationale for Biomarker Assessments

To demonstrate evidence of the biological activity of GDC-6599, biomarker assessments, before (i.e., randomization, pretreatment, baseline) and at various timepoints after treatment, will be used to identify biomarkers that may be predictive of response to GDC-6599 and/or demonstrate PD activity of GDC-6599, define PK/PD relationships, support selection of a recommended dosing regimen, and/or advance the understanding of the mechanism of action of GDC-6599 in patients on the basis of the following endpoints:

- Change from the baseline visit in biomarker levels in [redacted].
- Relationship among biomarker levels in [redacted].
- Relationship between biomarkers in [redacted]

During this study, [redacted] *[collected under prior versions of this protocol]*) will be collected. [redacted]

Additionally, blood samples will be collected for DNA extraction (optional) to enable identification of mutations in genes encoding that are associated with chronic cough and activity of TRPA1 in the airway or can increase the knowledge and understanding of disease biology.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation.

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

3.3.5 Rationale for Mannitol Challenge Test

Inhaled cough challenge models with agents that safely activate sensory neuron receptors such as TRPV1 and P2X3 are commonly performed to assess neuronal hypersensitivity, a hallmark of chronic cough and cough hypersensitivity syndrome, and to evaluate the mechanism of action of investigational therapeutics for these diseases (Morice et al. 2007; Song and Morice 2017). Activation of c-fibers with inhaled capsaicin evokes cough via TRPV1 in humans without significant bronchoconstriction, and therefore has been the most common cough challenge agent (Koskela et al. 2021; Mai et al. 2021). Activating TRPA1 ion channels in humans is more limited. TRPA1 can be stimulated by wide variety of natural products and environmental irritants but these are pungent to inhale, can cause occupational asthma, and/or are carcinogenic; acrolein in cigarette smoke, mustard oil (i.e., isothiocyanate), garlic, formalin, wasabi, and cinnamaldehyde (Belvisi et al. 2011). Due to the hydrophobic properties of TRPA1 agonists, they require dissolution in high amounts of ethanol and these amounts would be intolerable to patients with chronic cough. Cinnamaldehyde has been administered to healthy volunteers and guinea pigs, but has never been attempted in patients with asthma or chronic cough (Birrell et al. 2009). An alternative approach to stimulate TRPA1 would be to induce a change in osmolarity (e.g., with mannitol) and/or pH (e.g., with citric acid), though specificity of these challenges agents for TRPA1 is less understood. Changes in pH are known to activate TRPV1 and other acid sensing ion channels in addition to TRPA1 (Gu and Lee 2011; Mukhopadhyay et al. 2014; Joseph et al. 2021).

AHR is a key pathophysiological feature in asthma and eosinophilic COPD and is related to an increased airway smooth muscle contractility due to mast cell infiltration and eosinophilic airway inflammation. The mannitol challenge test is a clinical, indirect, osmotic bronchial challenge test using inhaled dry powder mannitol to assess the severity of AHR, a measure of asthma control, and is often used to aid the diagnosis of asthma (Sverrild et al. 2009) that correlates with the level of eosinophilic and mast cell airway inflammation that is highly predictive of the response to anti-inflammatory therapies such as inhaled corticosteroid (ICS) treatment (Lipworth et al. 2012; Anderson et al. 2016) or biologic therapies recently developed for the treatment of moderate severe asthma (Sverrild et al. 2021).

Inhaled mannitol has been shown to induce dose-dependent AHR in patients with asthma and COPD, but not in healthy volunteers (Koskela et al. 2004; Leuppi et al. 2005; Backer et al. 2020). Several studies have also demonstrated that inhalation of mannitol elicits cough in a dose-response manner and differentiates patients with CRC/UCC hypersensitivity syndrome in a disease population (Koskela et al. 2018; Nurmi et al. 2019).

The mechanism of mannitol-induced bronchoconstriction is not clearly understood. It is unknown whether mannitol-induced bronchoconstriction is due to direct activation of TRPA1 by mannitol as an irritant to sensory neurons or indirect activation due to the hyper-osmolar effect of mannitol causing mast cell degranulation and releasing inflammatory mediators (histamine, tryptase, prostaglandins) and immunomodulators, such as PGD2, capable of smooth muscle contraction and activation of TRPA1. In addition, coughing when inhaling mannitol is thought to occur due to i) dry powder inhalation stimulating mechanosensors; ii) changes in osmolarity; iii) bronchoconstriction; and iv) the release of histamine, prostaglandins from mast cells in the airways which can all directly sensitize and/or activate airway nerves and TRPA1 (Koskela et al. 2004; Anderson et al. 2016; Koskela et al. 2020). Thus, mannitol challenge could be a relevant disease model to explore the mechanism of action and efficacy of novel anti-tussive compounds.

This is relevant for TRPA1 antagonist because the TRPA1 receptor is sensitive to changes in osmolarity (Zhang et al. 2008) and blocking TRPA1 has shown to be reduce inflammation and bronchoconstriction in nonclinical models (Balestrini et al. 2021).

This study will *test whether mannitol-induced AHR and cough are TRPA1 dependent and will explore* mannitol-induced AHR and cough in different respiratory disease subsets. If mannitol is a TRPA1-responsive challenge agent, it may have utility in future clinical studies as a PD biomarker of TRPA1 activity. Furthermore, this study will instigate the relationship of *baseline cough hypersensitivity, measured by* mannitol-induced cough, with efficacy endpoints (e.g., 24-hour cough count) and inform the use of mannitol-induced AHR or cough as prognostic biomarkers for a personalized approach to treatment with a TRPA1-specific therapy such as GDC-6599.

3.3.6 Rationale for 24-Hour Cough Monitoring and Continuous Digital Cough Assessment

Cough will be assessed by the VitaloJAK semi-automated cough counting system. VitaloJAK is the only clinically validated, 510K-cleared, and Conformité Européenne-marked medical device system for the objective measurement of cough (Birring et al. 2008; Barton et al. 2012; Smith et al. 2021). VitaloJAK has been used to measure cough frequency as either a primary or secondary endpoint in several Phase II and III programs, including gefapixent, BAY1817080, and BLU-5937, targeting patients with UCC or CRC. The treatment effect in this study will be analyzed on the basis of cough frequency data (24-hour OCC) collected via VitaloJAK.

While VitaloJAK is the current gold standard for measuring cough frequency, it is limited to a maximum of 24-hour recordings. Previous placebo-controlled studies suggest there is significant day-to-day variability in 24-hour OCC that reduces the probability of detecting treatment differences based upon a single 24-hour data collection. [redacted]

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 80 patients with five distinct subsets of chronic cough will be enrolled in this study (Part A and Part B). Potential patients are eligible to be included in the study only if all of the general inclusion criteria (Section 4.1.1.1) and the criteria for their respective disease background (Section 4.1.1.2 or Section 4.1.1.4) are met.

Table 2 Planned Study Enrollment

Study	Cohort	*Approximate* No. of Patients per Cohort
Part A	CRC with *asthma ± atopy*	*30*
	UCC	*30*
Part B	CRC COPD *± CB*	*20*
Total enrollment		80

COPD = chronic obstructive pulmonary disease; COPD *± CB* = chronic obstructive pulmonary disease with *or without* chronic bronchitis; CRC = chronic refractory cough; UCC = unexplained chronic chough.

4.1.1 Inclusion Criteria

4.1.1.1 General Inclusion Criteria for All Patients

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–80 years at time of signing Informed Consent Form (except patients with COPD ≥ 40 years old)

- Ability to comply with the study protocol
- Body mass index (BMI) of 17–35 kg/m^2 at screening
- *A Persistent cough that has lasted for at least 1 year, and refractory* despite optimized treatment for asthma, COPD, *GERD,* or UCC for at least *12 weeks* (see CHEST 2018/ERS 2020 guidelines [Irwin et al. 2018; Morice et al. 2020].
- Chest X-ray or computed tomography (CT) scan thorax within 5 years prior to screening *visits* that confirms*, in the opinion of the investigator,* the absence of any clinically significant abnormality contributing to the chronic cough*, with the exception of COPD for patients with CRC COPD with or without CB (see Section 4.1.1.4)*
- Cough severity VAS score ≥40 at screening
- Pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥60% of predicted value at screening
- Mannitol CDR ≥12 coughs per 100 mg of mannitol determined at screening mannitol challenge test, based on manual cough counting
- Demonstrated ability to use and comply with electronic patient-reported outcome (ePRO) requirements, defined as completion of all questions on at least 2 out of 7 consecutive days within the 14 days during screening

  Patients unable to demonstrate compliance with completing the electronic daily assessments (Numeric Response Scale [NRS] and VAS on ePRO) within the first 2 weeks of screening will be screen failed. Patients will have the opportunity to demonstrate ePRO compliance if re-screened.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for [redacted] after the final dose of study drug, or for the period required by local guidelines or regulations, whichever is longer.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.1.2 Inclusion Criteria for Patients with CRC with Atopic Asthma or Patients with CRC with Non-Atopic Asthma (Part A)

Patients *with CRC with atopic asthma or patients with CRC with non-atopic asthma* must meet the following criteria for study entry:

- Physician diagnosis of asthma for *≥12 weeks* based upon GINA STEP 2–5
- Stable treatment with ICS therapy (GINA STEP 2) or ICS therapy and at least one additional controller (GINA STEP 3–5) for *≥12 weeks*
- Patients with atopic asthma, based upon historic record of positive test for atopy (if available), or confirmed at screening by *any positive test result from a panel of standard allergens including cat dander, dog dander, cockroach, dust mite, mold, and relevant local allergens, as determined through use of ImmunoCAP™ Specific IgE test, skin prick test, or radioallergosorbent test (RAST)*
- Patients with non-atopic asthma, based upon historic record of negative test for atopy (if available), or confirmed at screening by *negative test result across chosen atopy testing panel and no history or symptoms suggesting atopy*
- *No history of smoking or* former smoker with *smoking history of <*20 pack-years or equivalent history

  Smoking is defined as use of inhaled tobacco or cannabis products (e.g., cigarettes, cigars, electronic cigarettes, vaporizing devices, or pipes).

  A former smoker is defined as someone with smoking history who has not used inhaled tobacco or cannabis products within 6 months prior to screening.

4.1.1.3 *Inclusion Criteria for Patients with UCC (Part A)*

Patients with UCC must meet the following criteria for study entry:

- *Diagnosis of UCC*
- *No history of smoking or former smoker with smoking history of <20 pack-years or equivalent history*

  Smoking is defined as use of inhaled tobacco or cannabis products (e.g., cigarettes, cigars, electronic cigarettes, vaporizing devices, or pipes).

  A former smoker is defined as someone with smoking history who has not used inhaled tobacco or cannabis products within 6 months prior to screening.

4.1.1.4 Inclusion Criteria for Patients with CRC COPD-CB or Patients with CRC COPD (Part B)

Patients *with CRC COPD* must meet the following criteria for study entry:

- Diagnosis of COPD GOLD I–II ± CB

  CB assessed by single question: Have you had productive cough (sputum/mucus) daily for the past 4 weeks or longer?

- Stable background treatment for ≥ 12 weeks prior to screening

  On an eligible bronchodilator medication (long-acting β-agonists [LABAs], long-acting muscarinic antagonists, or both) *≥12 weeks* prior to screening and/or on stable ICS therapy for *≥12 weeks* prior to screening

- Former smoker with ≥ 10 pack-years or equivalent history *who has not used inhaled tobacco or cannabis products (e.g., cigarettes, cigars, electronic cigarettes, vaporizing devices, or pipes)* within 6 months prior to screening

- Post-bronchodilator FEV_1/forced vital capacity (FVC) ratio ≤ 0.70 at screening

- Chest X-ray or CT scan within 6 months prior to screening visit or during the screening period (prior to randomization [Study Visit 2]), that confirms the absence of clinically significant lung disease besides COPD

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intention of becoming pregnant during the study or within [redacted] after the final dose of GDC-6599

  Women of childbearing potential must have a negative serum pregnancy test result at screening and a negative urine pregnancy test within 1 day prior to initiation of study drug.

- History of diagnosed bleeding diathesis or easy bruising or bleeding (i.e., bruising or bleeding out of proportion to the degree of trauma)

- Post-bronchodilator FEV_1/FVC ratio < 0.60 at screening (patients with CRC asthma and UCC only: Part A)

- Acute exacerbations *of asthma or COPD* within 8 weeks prior to screening

- Use of oral *or* systemic corticosteroids *for the treatment of respiratory diseases, including cough,* within 8 weeks prior to screening

  Continued, chronic use of oral or systemic corticosteroids for non-respiratory conditions is permitted, provided patient has been receiving a stable treatment regimen for at least 8 weeks prior to screening and, in the opinion of the investigator, is likely to remain on the stable treatment regimen through completion of the study.

- [redacted]

- Initiation of proton-pump inhibitor (PPI) therapy within 8 weeks prior to screening

- History of significant hepatic impairment, defined as Child-Pugh Class B or C, corresponding to a Child-Turcotte-Pugh Score ≥7
- History of aspiration pneumonia
- Respiratory infection (including upper respiratory infection)*, known COVID-19 infection, persistent symptoms of known prior COVID-19 infection, and/or known positive COVID-19 test* within 8 weeks prior to screening *and randomization*

  COVID-19 testing is not required for participation in the study unless required by local regulations or institutional policies.
- Positive HIV antibody test at screening
- Positive hepatitis B surface antigen (hBsAg) at screening
- Positive hepatitis C virus (HCV) antibody test followed by a positive HCV RNA test at screening

  The HCV RNA test must be performed if a patient has a positive HCV antibody test at screening to determine if the patient has an HCV infection.
- Treatment with investigational therapy within 28 days or 5 drug-elimination half-lives (if known), whichever is longer, prior to initiation of study drug
- Treatment with any strong inhibitor or inducer of CYP3A within 28 days or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study drug
- [redacted]
- Treatment with any vaccine within 7 days prior to initiation of study drug or a scheduled vaccination during study period (through follow-up/early termination visit)
- Treatment with angiotensin-converting enzyme (ACE) inhibitor within *8* weeks prior to screening
- Treatment with opioids (including codeine), pregabalin, gabapentin, amitriptyline, or nortriptyline for the treatment of cough within 2 weeks prior to screening

  Treatment with any of these medications for indications other than chronic cough is permitted, provided the patient is receiving a stable treatment regimen for at least 2 weeks prior to screening and, in the opinion of the investigator, is likely to remain on the stable treatment regimen through completion of the study.
- *Treatment with dextromethorphan, guaifenesin, benzonatate, and any other over-the-counter or prescription medication containing an anti-tussive or expectorant for the treatment of cough within 2 weeks prior to screening*
- History of serious adverse reaction or serious hypersensitivity to any drug or the study drug formulation excipients
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Planned major surgical intervention that may require general anesthetic and/or hospital stay during the study

- Serious infection requiring oral or IV antibiotics within 14 days prior to screening or randomization
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- History of malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix or non-melanoma skin carcinoma
- Any of the following clinical laboratory values at screening (even if not considered clinically significant):
  - PT (INR) $>$ upper limit of normal (ULN), PTT $>$ ULN or platelet $<$ lower limit of normal (LLN)
  - ALT or AST $>$ ULN
  - Total bilirubin $>$ ULN; patients with Gilbert syndrome may enroll provided total bilirubin $\leq 1.5 \times$ ULN and direct (conjugated) bilirubin is $\leq$ ULN

  Laboratory testing may be repeated one time during screening if the initial results are outside the normal range specified by the laboratory performing the test or outside the ranges specified above.
- QT interval corrected through use of Fridericia's formula (QTcF) $>$ 450 ms

  If the initial QTcF $>$ 450 ms, the ECG should be repeated at least 30 minutes after the first ECG. The patient may be enrolled if second QTcF $\leq$ 450 ms.
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), unstable coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing) within last 12 months, clinically significant electrolyte abnormalities, or family history of sudden unexplained death or long QT syndrome
- Current treatment with medications that are well known to prolong the QT interval *within 1 month prior to screening*

  Refer to Appendix 12 for a list of drugs associated with QT prolongation.
- If stipulated by local or national laws: employed by the site, the Sponsor, or Sponsor representatives or financially dependent on, or related to, an employee of the site, the Sponsor, or Sponsor representatives
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction within last 12 months
- Known allergic sensitivity or reaction to adhesives, such as those used for VitaloJAK chest sensor application, that in the opinion of the investigator may impact the ability of the patient to complete the study

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a randomized, double-blind, crossover study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS). Patients will be randomized in a 1:1 ratio to receive [redacted] mg GDC-6599 or placebo [redacted] in Treatment Period 1. After a 14-day washout period, patients will begin Treatment Period 2, during which the opposite treatment received in Treatment Period 1 will be administered.

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider*, and members of the IMC as specified in the IMC Charter.*

While PK samples must be collected during both treatment periods to maintain the blinding of treatment assignment, PK assay results for the placebo treatment period are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from the placebo treatment period will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing).

If unblinding *becomes* necessary *because of* a medical emergency (e.g., serious adverse event for which management might be affected by knowledge of *the participant's* treatment assignment), the investigator will be able to break the treatment code *via the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code in an emergency situation. However, the Medical Monitor should be informed that the treatment code has been broken.*

The investigator will also be able to break the treatment code to determine the suitability of subsequent medical care for a participant. However, approval must be obtained from the Sponsor Medical Monitor if the investigator wants to break the treatment code to determine a participant's eligibility for a subsequent clinical trial testing investigational medicinal products or procedures. The investigator must contact the Sponsor Medical Monitor prior to breaking the treatment code for any reason other than a medical emergency. The investigator should document and provide an explanation for any non-emergency unblinding.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to an investigational medicinal product (IMP; defined in Section 4.3).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are GDC-6599 and mannitol, provided in the form of a manufactured kit by the name of Aridol®/Osmohale®.

Appendix 11 identifies all IMP and NIMP for this study.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 GDC-6599 and Placebo

GDC-6599 and matching placebo will be supplied and formulated by the Sponsor as film-coated tablets, with GDC-6599 provided in [redacted] dose. For information on the GDC-6599 formulation, see the pharmacy manual and GDC-6599 Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

GDC-6599 or placebo will be administered orally at a dose of [redacted]. *GDC-6599 or placebo tablets should be taken approximately* [redacted]. *For Visit 2 (Day 1), Visit 4 (Day 14), Visit 5 (Day 30), and Visit 7 (Day 43),* [redacted] *Patients may self-administer* [redacted] *for Visit 3 (Day 7) and Visit 6 (Day 36). Patients will self-administer all other doses of study drug at home.*

All active and placebo tablets will be administered by mouth, followed immediately with water. *The tablets should be swallowed whole; they should not be chewed, cut, broken, or crushed.* Study drug may be taken with or without food. *If a dose of study drug is missed (i.e. delayed by more than 4 hours) or if vomiting occurs when the dose is taken, the patient should resume dosing with the next scheduled dose without compensating for the missed dose.*

For doses administered in the clinic, compliance will be assessed by a visual check of the mouth and hand performed by site staff. For self-administered doses, patients will be required to record the time they took each dose every day in a study drug compliance electronic diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their study drug compliance diaries to the clinic at specified study visits (see schedule of activities in Appendix 1). Compliance will be assessed by reviewing diaries and counting returned tablets.

Refer to the pharmacy manual for detailed instructions on drug preparation and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.11.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.3.1.

4.3.3 Mannitol Challenge Test

The mannitol challenge test (Aridol®/Osmohale®) is a commercially approved bronchial challenge test kit containing prefilled mannitol capsules and a handheld dry powder inhaler device. For additional information on the formulation, packaging, and handling of mannitol dry inhalation powder, see the local prescribing information.

4.3.4 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs 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 staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the GDC-6599 Investigator's Brochure for information on IMP handling. Tablets should not be stored above 30°C. Accountability will be secured according to local work instructions.

4.3.5 Continued Access to GDC-6599

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Genentech IMP (GDC-6599) or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing GDC-6599 in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

https://assets.cwp.roche.com/f/176343/x/92d6b13ee6/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 14 days prior to initiation of study drug to the safety follow-up Visit 8/early termination visit. All such medications should be reported to the investigator and recorded on the Concomitant Medication eCRF *or Adverse Event or Intercurrent Illness eCRF.*

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of < 1% per year (see Section 4.1.1)
- Hormone-replacement therapy
- Medications necessary to treat underlying disease (asthma/COPD) except those that are restricted prior to mannitol challenge test (see Section 4.4.4)

- *Opioids (including codeine), pregabalin, gabapentin, amitriptyline, or nortriptyline for indications other than chronic cough are permitted, provided patients are receiving a stable treatment regimen for at least 2 weeks prior to screening and, in the opinion of the investigator, are likely to remain on the stable treatment regimen through completion of the study*
- *Oral or systemic corticosteroids for non-respiratory conditions is permitted, provided patients have been receiving a stable treatment regimen for at least 8 weeks prior to screening and, in the opinion of the investigator, are likely to remain on the stable treatment regimen through completion of the study*
- *Oral corticosteroids as rescue therapy for the treatment of acute exacerbations is permitted*
- *PPI therapy is permitted, provided treatment was initiated at least 8 weeks prior to screening*
- Treatments for conditions associated with chronic cough, such as GERD, asthma, upper airway cough syndrome (formerly called post-nasal drip) are permitted, if patients have been treated for at least *12 weeks* for these comorbid conditions and are receiving a stable treatment regimen for at least 2 weeks prior to screening and, in the opinion of the investigator, are likely to remain on the stable treatment regimen through completion of the study

Possible treatment options for comorbid conditions are provided in Table 3. As this list in not meant to be comprehensive, consult Sponsor for additional information.

Table 3 Treatment for Comorbid Conditions of Chronic Chough

Condition	Treatment
GERD	Anti-reflux therapy (PPI or H_2 blocker) and/or pro-kinetic agents
Asthma	Bronchodilators, ICS
COPD	Bronchodilators, ICS

COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroid; PPI = proton-pump inhibitor.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice.

4.4.2 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days or 5 drug-elimination half-lives (if known), whichever is longer, prior to initiation of study treatment and during study treatment

- Treatment with any strong inhibitor or inducer of CYP3A within 28 days or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study drug is prohibited. The use of any strong CYP3A inhibitor or inducer during the study is prohibited.

  Known strong CYP3A inducers: rifampin (also known as rifampicin), mitotane, avasimibe, rifapentine, apalutamide, phenytoin, carbamazepine, enzalutamide, ivosidenib, St John's wort, lumacaftor

  Known strong CYP3A inhibitors: Please refer to the Indiana University Drug Interactions Flockhart Table™ (Flockhart et al. 2021)
- ACE inhibitors are prohibited within *8* weeks prior to screening through completion of the study at Visit 8.
- Use of opioids (including codeine), pregabalin, gabapentin, amitriptyline, or nortriptyline for the treatment of cough is prohibited within 2 weeks prior to screening through *the end of the second treatment period*.

  Treatment with any of these medications for indications other than chronic cough is permitted, provided patients are receiving a stable treatment regimen for at least 2 weeks prior to screening and, in the opinion of the investigator, are likely to remain on the stable treatment regimen through completion of the study.
- Use of dextromethorphan, guaifenesin, benzonatate, and any other over-the-counter *cough-suppressant* or prescription medication *containing an anti-tussive or expectorant* for the treatment of cough is prohibited within 2 weeks prior to screening through *the end of the second treatment period*.
- *Use of oral or systemic corticosteroids for the treatment of respiratory disease, including cough, is prohibited within 8 weeks prior to screening through the end of the second treatment period.*

  Continued, chronic use of oral or systemic corticosteroids for non-respiratory conditions is permitted, provided treatment was initiated at least 8 weeks prior to screening.

  Oral corticosteroids as rescue therapy for the treatment of acute exacerbations is permitted during the study.
- [redacted]
- *Initiation of proton-pump inhibitor (PPI) therapy is prohibited within 8 weeks prior to screening and is prohibited through the end of the second treatment period.*

  Continued use of PPI therapy during the study is permitted, provided treatment was initiated at least 8 weeks prior to screening.
- *Treatment with medications that are well known to prolong the QT interval is prohibited from within 1 month prior to screening through the completion of the study at Visit 8.*

  Refer to Appendix 12 for a list of drugs associated with QT prolongation.

- *Treatment with xanthines (e.g., theophylline, oxtriphylline) is prohibited within 24 hours prior to mannitol challenge tests.*
- Initiation of new dietary and herbal remedies which do not contain an active anti-tussive or expectorant (e.g., lozenges, drops, teas, drinks, and similar treatments) is prohibited, unless the supplement is not expected to interfere with the study, as determined by the investigator in consultation with the Sponsor.

  Patients who have been using such dietary and herbal remedies on a regular basis for at least 2 weeks prior to screening are eligible to enroll.

Patients requiring a prohibited therapy will be discontinued from study treatment and will undergo follow-up assessments as described in Appendix 1 .

4.4.3 Prohibited Food

Use of the following foods is prohibited for all patients as described below:

- Consumption of liquid or food containing grapefruit, Seville orange, pomelo, or tangelo from 10 days prior to the first study visit until 72 hours after the final dose of study drug
- Consumption of alcohol from 24 hours prior to and 24 hours following each study visit

4.4.4 Additional Restrictions

Activity restrictions:

- Patients should abstain from strenuous exercise and avoid noisy environments (e.g., hair dryer, lawn equipment, open windows while driving, cinemas, listening to music, etc.) while the VitaloJAK cough monitor is attached over a 24-hour period. However, patients may participate in light recreational activities (e.g., watching television at a low volume, reading).
- Patients should not allow the VitaloJAK cough monitor, microphone, or chest sensor to get wet. Thus, they must avoid bathing or showering for the duration of the 24-hour recording.

  The VitaloJAK chest sensor will be applied to the patient's chest with an adhesive (sticky pad). If the patient has a known allergic sensitivity or reaction to adhesives, and in the opinion of the investigator the sensitivity or reaction is severe enough to impact the ability of the patient to complete the study, the patient should not be enrolled in this study.

  See the VitaloJAK site manual for further details.
- Patients should avoid vigorous exercise on the day of mannitol challenge test prior to administration.
- Patients should not consume caffeine within 12 hours prior to each mannitol challenge test.

Medication restrictions before provocation with mannitol:

- SABAs (short-acting β-agonists) within 8 hours prior to each mannitol challenge
- ICS within 12 hours prior to each mannitol challenge
- Ipratropium bromide within 12 hours prior to each mannitol challenge
- Non-steroidal anti-inflammatory medications within 12 hours prior to each mannitol challenge test.
- Twice daily LABAs or ICS/LABAs within 24 hours prior to each mannitol challenge
- *Xanthines (e.g., theophylline, oxtriphylline) within 24 hours prior to each mannitol challenge*
- Tiotropium bromide within 72 hours prior to each mannitol challenge
- Oral antihistamines within 72 hours prior to each mannitol challenge
- Leukotriene-Modifiers within 4 days prior to each mannitol challenge

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

At applicable sites, certain study assessments such as blood draws may be performed by an MN professional at the patient's home or another suitable location to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Appendix 1) will specify the assessments that may be performed by an MN professional.

4.5.1 Informed Consent Forms and Screening Records

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a detailed record of all patients screened, to document eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), historical record of post-bronchodilator reversibility of FEV_1 or documented methacholine positive test, history of acute exacerbations (asthma or COPD), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 14 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data, including age and sex, will be also recorded at baseline, along with self-reported race/ethnicity, sexual orientation, and gender identity for patients willing to provide this information (U.S. sites only).

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Sensory neurologic examinations, including assessment of light touch, pain, vibration, temperature, and two-point discriminative sensations, will be performed at screening and other specified timepoints to identify potential changes in the peripheral sensory system. TPRA1 is expressed on peripheral terminals of nociceptive primary sensory neurons, where it is involved in the transduction of potentially harmful stimuli. In addition, TRPA1 is involved in amplification of nociceptive transmission in the central terminals of nociceptive primary sensory neurons.

New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure (BP) while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Mannitol Challenge Test

The mannitol challenge test is a commercially approved bronchial challenge test kit containing pre-filled mannitol capsules and a handheld dry powder inhaler device. During a mannitol challenge test, patients will orally inhale increasing doses of mannitol. After each dose, airway parameters will be measured by spirometry. Inhalation of mannitol doses will continue until all doses (cumulative 635 mg) are inhaled*, there is a ≥15% decrease in FEV_1 relative to baseline,* or there is a *≥10% decrease in FEV_1* between two successive doses. *The mannitol challenge test is required at Study Visit 1 (screening) and optional at Study Visits 4 and 7 (see Section 4.5.14)*. Details regarding conduct of mannitol challenge are provided in the mannitol challenge test guidance.

4.5.6 Cough Monitoring

Objective cough counting will be conducted as per the study's pulmonary function and cough monitoring guidance documents, in addition to standard manual methods of counting during the mannitol challenge tests (Koskela et al. 2004; Koskela et al. 2018). Cough numbers will be assessed by the VitaloJAK (Vitalograph Inc.) semi-automated cough-monitoring system. The VitaloJAK device will record ambulatory audio for 24 hours from two channels, a lapel microphone (air) and a chest-facing sensor (skin). A software algorithm will remove non-cough sounds from the 24-hour audio recordings, compressing the files to less than 10% (on average) of the original length enabling manual analysis to be completed more quickly. The recordings will be reviewed by trained Vitalograph analysts who will count individual explosive cough sounds, yielding hourly and 24-hour OCCs.

The VitaloJAK counting device will be provided to all study sites. The VitaloJAK device will be used to record *spontaneous coughs during for 24 hours on the first day of screening, for 24 hours prior to the first dose of study drug of each treatment period, and for 24 hours following each optional mannitol challenge test during each treatment period (or for 24 hours beginning approximately 3 hours after study drug administration, if mannitol challenge test is not performed),* as outlined in the schedule of assessments (Appendix 1). The pulmonary function and cough monitoring guidance *documents* will include information on equipment, procedures, patient instructions, and precautions regarding the use of the VitaloJAK. Cough monitoring will be performed per the study's cough monitoring guidance *documents*. Required training on equipment use and data transfer methods will be provided.

[redacted]

[redacted]

[redacted]

4.5.7 Spirometry

Spirometry, including the procedure for mannitol challenge testing, will be conducted as per the study's pulmonary function testing manual which is based on the American Thoracic Society (ATS)/European Respiratory Society (ERS) Consensus Statement "Standardization of Spirometry 2019 Update" (Graham et al. 2019). The guidance will include information on equipment, procedures, patient instructions, and precautions. Spirometry will be performed on a centralized spirometry system (provided to all sites by the spirometry vendor), configured to the requirements of the study, and in accordance with ATS/ERS guidelines. Spirometric measures to be collected will include FEV_1 and FVC values as well as flow−volume and volume-time curves. The Global Lung Function Initiative (GLI) dataset (Quanjer et al. 2012) will be used to calculate percent-predicted FEV_1 and FVC values. The GLI data sets have been standardized on the basis of key demographic information that includes ethnicity and race. It is therefore necessary to collect patient race/ethnicity to ensure that the most appropriate reference equation is used to establish the predicted values.

Acceptability *or usability* of the spirometry data from the computerized configured system, including the graphic representations of the maneuvers, will be determined by over-readers blinded to study drug treatment. Calculations for the reproducibility of the acceptable maneuvers will be performed and reviewed centrally by over-readers *and/or the Medical Monitor* blinded to study drug treatment and/or the Medical Monitor.

Spirometry data may be used if it does not meet the acceptability and reproducibility criteria but represents the patients' best efforts and meets the ATS/ERS usability criterion, after discussion between the investigator and the Medical Monitor, as applicable.

Patients must be aware that medications containing bronchodilators may affect spirometry and must be withheld until assessments are completed on the day of the study visits. The last dose of SABAs must be administered at least 8 hours before testing and the last dose of LABAs must administered at least 24 hours prior to testing. Pre- and post-bronchodilator spirometry will be assessed during screening and at subsequent visits according to the schedules of assessments in Appendix 1. Study-specific training on equipment use, system calibration, and data storage and transfer will be provided by the Sponsor.

4.5.8 Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide (FeNO) is a volatile marker of airway inflammation and has been demonstrated to decrease with ICS treatment. Measurement of FeNO will be performed through the use of a standard nitric oxide machine, in accordance with guidelines published by the ATS (training and guidance to be provided separately) (Dweik et al. 2011). FeNO measurement must be performed before spirometry testing. To minimize the effect of diurnal variation, FeNO measurements should be performed at approximately the same time of day (±2 hours) as the first measurement. Patients should avoid consumption of nitrate-rich foods (such as processed meats [bacon, lunch meat, hot dog, and sausage], spinach, green beans, broccoli, and cauliflower) for at least 8 hours prior to FeNO measurement and avoid all food or drink and strenuous exercise at least 1 hour before FeNO measurement.

[redacted]

4.5.10 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Urine pregnancy test

Samples for the following laboratory tests will be sent to the study site's local laboratory or to one or several central laboratories for analysis:

- *ImmunoCAP Specific IgE test panel, skin prick test, or RAST for specific IgE against standard allergens for cat dander, dog dander, cockroach, dust mite, mold, and relevant local allergens*

  The ImmunoCAP *Specific IgE* test panel, *skin prick test, or RAST* is required only for patients *with asthma* who do not have confirmed atopic versus non-atopic status in their medical records. Patient eligibility may be determined by medical history alone (see Section 4.1.1.2).

Samples for the following laboratory tests will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and percentage and absolute differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate, sodium, potassium, chloride, glucose, urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and LDH
- Coagulation: INR, aPTT, and PT
- Vitamin K–dependent coagulation factors: Factors II, VII, IX, X, and protein C and S
- HIV serology: HIV-1/2 antibody
- Hepatitis B virus serology: HBsAg
- HCV serology: HCV antibody for all patients; HCV RNA for patients with a positive HCV antibody test

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- Follicle-stimulating hormone (FSH) at screening to confirm postmenopausal state, if required per local guidelines.
- Serum pregnancy test

  All women *of childbearing potential* will have a serum pregnancy test at screening. Urine or serum pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  Test for FSH may be performed at screening to confirm postmenopausal state, if required per local guidelines.
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood), and urine creatinine

  Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) should be performed if the dipstick is abnormal.

- COVID-19 testing at screening

  COVID-19 testing is to be performed as per local regulations or institutional policies.

[redacted] for exploratory research on biomarkers and biomarker assay development. Exploratory biomarker research may include, but will not be limited to [redacted]. *Research may involve* whole genome sequencing (WGS) or whole exome sequencing (WES) of blood samples, but only at participating sites (see Section 4.5.13).

Venous blood samples will be collected for measurement of plasma concentrations of GDC-6599 (by validated assay), as specified in the schedule of activities. The actual date and time (24-hour clock time) of each sample will be recorded. Plasma samples collected for PK analysis may be needed for PK assay development and validation and evaluation of metabolites; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. *Previously collected sputum* samples may also be analyzed for GDC-6599 concentration.

[redacted] including those collected from patients who do not enroll in the study, may be used for research related to the development of disease-related tests or tools.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.15), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- [redacted] collected for biomarker research and biomarker assay development will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the exception of tissue samples that undergo WGS or WES, which will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the

samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Data generated from samples collected for exploratory biomarker research will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients. In addition, given the complexity and exploratory nature of biomarker analyses, data derived from these analyses will generally not be provided to investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.11 Electrocardiograms

A single 12-lead ECG will be performed at screening to confirm eligibility. If the initial QTcF $>$ 450 ms, the ECG should be repeated at least 30 minutes after the first ECG. The patient may be enrolled if second QTcF $\leq$ 450 ms. Thereafter, a single 12-lead ECG recording must be obtained for each specified timepoint. Single 12-lead ECG recordings may also be obtained at unscheduled timepoints. Triplicate ECGs are not required; however, ECGs with artifacts that may interfere with interpretation should be repeated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular timepoint the mean QTcF is $>$ 500 ms and/or $>$ 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and

ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 5.1.3.3. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.12 Clinical Outcome Assessments

The following PRO instruments will be completed to characterize the patient-reported symptoms and impact associated with chronic cough in patients with CRC with asthma, CRC with COPD, or UCC and to assess the treatment benefit across the study populations and patient experience of GDC-6599: [redacted] VAS, and NRS. The [redacted] will be completed to characterize patient-reported symptoms in patients with CRC asthma. On days when multiple PRO assessments are scheduled, the order of questionnaire completion is the following: [redacted], VAS, and NRS.

4.5.12.1 Data Collection Methods for Clinical Outcome Assessments

The [redacted], and VAS will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). The NRS and VAS will be self-administered at home via ePRO on a daily basis according to the schedule of assessments. At the clinic, PRO assessments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor (note that [redacted] will be completed on paper with responses captured in the ePRO database). The device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

Patients should be given the following instructions for completing PRO instruments at home:

- Patients should complete the instruments in a quiet area with minimal distractions and disruptions.
- Patients should answer questions to the best of their ability; there are no right or wrong answers.

- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 10 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.12.2 Description of Clinical Outcome Assessment Instruments

[redacted]

[redacted]

.

Visual Analog Scale

The VAS is a single-item rating used for the subjective assessment of cough severity. Patients will be asked to indicate the severity of their cough by marking a line on a scale between anchor statements of 'no cough' and 'worst cough' using a recall period of 'today'. A copy of the VAS is provided in Appendix 6.

Numeric Response Scale

The NRS is a single-item measure of cough severity. Patients will be asked to rate the severity of their cough from 0 (no cough) to 10 (worst cough) using a recall period of 'today'. A copy of the NRS is provided in Appendix 7.

4.5.13 Blood Samples for Whole Genome Sequencing *or Whole Exome Sequencing* (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will include exploration of germline variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.13) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Refer to Section 4.5.10 for details on use of samples after patient withdrawal and confidentiality standards for data.

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.14 *Optional Mannitol Challenge Tests*

Consenting patients will undergo optional mannitol challenge tests during each treatment period at Study Visits 4 and 7. Each mannitol challenge test is to be performed at least 2.5 hours after study drug administration. Details on the mannitol challenge test are provided in Section 4.5.5 and in the mannitol challenge test guidance. See Section 4.5.6 for details on cough monitoring during the challenges. Medication restrictions prior to the mannitol challenge are provided in Section 4.4.4.

The Informed Consent Form will contain a separate section that addresses the optional mannitol challenge tests. A separate, specific signature will be required to document a patient's agreement to undergo the optional mannitol challenge tests. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.10. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.10 for details on duration of sample storage,

use of samples after subject withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.15 Optional Samples for Research Biosample Repository

4.5.15.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.15.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.15.2) will not be applicable at that site.

4.5.15.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to GDC-6599 or TRPA1, diseases, or drug safety:

- [redacted] and any derivatives thereof (e.g., DNA, RNA, proteins, peptides); see [redacted] for schedule of sample collection.

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is

increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.15.4 Data Protection, Use, and Sharing

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients, unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some

samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.15.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.15.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.15.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

A patient must permanently discontinue study treatment if any of the following criteria are met:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Serious adverse event related to study drug in the opinion of the investigator and Sponsor
- Clinically significant Grade ≥ 3 adverse event, as determined by the investigator, related to study drug
- Persistent (> 2 hours) Grade 1 bleeding
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- INR ≥ 4 and Grade 3 or Grade 4 bleeding
- [redacted]
- ALT or AST elevation ≥ 3 × ULN in combination with either total bilirubin ≥ 2 × ULN or clinical jaundice (Hy's Law; see Section 5.3.5.6)
- Episode of torsades de pointes (unless there is a clear alternative cause for the changes)

- Sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms and > 60 ms longer than the baseline value or sustained QTcF > 515 ms (unless there is a clear alternative cause for the changes)
- Patient requirement for a prohibited therapy (see Section 4.4.2)

The IMC will review any event suggestive of a significant safety risk to patients. Study treatment for all enrolled patients may be paused or discontinued pending IMC review if any of the following criteria are met in two or more patients:

- Elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice as defined by Hy's law (see Section 5.3.5.6)
- Sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms and > 60 ms longer than the baseline value or sustained QTcF > 515 ms (unless there is a clear alternative cause for the changes)
- Episode of torsades de pointes (unless there is a clear alternative cause for the changes)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment completion or treatment discontinuation [redacted] days after the final dose of study drug.

Refer to the schedule of activities (see Appendix 1) for details on follow-up assessments to be performed for patients who permanently discontinue study treatment. If a patient requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

4.6.2 Patient Discontinuation from the Study

Patients will return to the clinic for a study completion or study discontinuation visit at [redacted] after the last dose of study drug.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up

- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Any event or scenario leading to permanent cessation of dosing in all patients (Section 4.6.1) and for which the IMC (in consultation with the investigator) cannot identify an adequate risk mitigation measure or therapeutic margin
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

GDC-6599 is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on nonclinical data and clinical experience with GDC-6599 in the *completed* first-in-human Phase Ia/b SAD and MAD study in healthy volunteers (Study GA43010).

However, the full spectrum of risks in humans has not yet been fully characterized. Therefore, the anticipated potential/theoretical risks for GDC-6599 outlined below are based on the anticipated mechanism of action and results from nonclinical studies.

Please refer to GDC-6599 Investigator's Brochure for a complete summary of safety information.

The mannitol challenge test is a commercially approved bronchial challenge test kit containing prefilled mannitol capsules and a handheld dry powder inhaler device. Please refer to local prescribing information for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities (see Section 4.1). Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with GDC-6599

[redacted]

[redacted]

[redacted]

5.1.1.2 Impaired Cough Reflex

Ion channels of the TRP class are important in the afferent sensory loop of the cough reflex and in the heightened cough sensitivity seen in disease. There is growing evidence for both TRPV1 and TRPA1 in peripheral sensitization and cough (Morice et al. 2014). Specifically, TRPA1 is expressed in small diameter, nociceptive neurons in the airways, where its activation by cold temperatures and environmental irritants may contribute to the perception of noxious stimuli and the stimulation of vagal sensory afferent neurons leading to central reflexes including cough, which is necessary to remove the foreign material from the respiratory tract (Grace et al. 2011). For this reason, there is a theoretical risk that inhibition of TRPA1 may impair normal cough reflexes.

As a result, antagonists of TRPA1, such as GDC-6599, may reduce sensitivity to foreign material in the airways, which may increase the risk of aspiration pneumonitis and lower respiratory tract infections. Individuals with a history of recurrent lower respiratory tract infections, such as pneumonia, have been shown to have a decreased response to capsaicin, an agonist of TRPV1 (Niimi et al. 2003). It is unknown whether this association is unique to TRPV1 or generalizable to other TRP-class ion channels. Conversely, in patients with a history of severe asthma, increased sensitivity to capsaicin was associated with poorer asthma control, suggesting that in pathogenic processes such as asthma, the cough reflex is maladaptive (Kanemitsu et al. 2020).

Animal studies of GDC-6599 found no evidence of impairment in cough or increased risk of lower respiratory tract infections. However, animals included in toxicity studies are healthy, are prescreened for certain infectious agents with negative test results before study start, and are housed in a controlled laboratory environment that limits the risks of infections. Thus, the absence of findings may not be predictive of the risk for human subjects.

Patients with a history of aspiration will be excluded from participating in the study (see Section 4.1.2), and patients will be closely monitored for respiratory tract infections.

Guidelines for management of patients who develop lower respiratory tract infections are provided in Section 5.1.3.2.

[redacted]

[redacted]

[redacted]

5.1.2 Potential Risks Associated with Mannitol Challenge Test

Investigators should be aware of the risks associated with the mannitol challenge test and guidelines for managing those risks. Please refer to the local prescribing guidelines for the mannitol challenge test (Aridol®/Osmohale®) for full information.

5.1.2.1 Severe Bronchospasm

Mannitol acts as a bronchoconstrictor and may cause severe bronchospasms in susceptible patients. The test should only be conducted by trained professionals under the supervision of a physician familiar with all aspects of the bronchial challenge test and the management of acute bronchospasm. Patients should not be left unattended during the bronchial challenge test. Medications and equipment to treat severe bronchospasm must be present in the testing area. If severe bronchospasm occurs, it should be treated immediately by administration of a SABA. Because of the potential for severe bronchoconstriction, the bronchial challenge testing with mannitol should not be performed in any patient with very low baseline pulmonary function tests (e.g., $FEV_1 < 1-1.5$ liters or $< 60\%$ of the predicted values)

If a patient has a $\geq 10\%$ reduction in FEV_1 (from pre-challenge FEV_1) on administration of the 0 mg capsule, the mannitol challenge test should be discontinued and the patient should be given a dose of an inhaled SABA and monitored accordingly.

Patients with either a positive response to bronchial challenge testing with mannitol or significant respiratory symptoms should receive an inhaled SABA. Patients should be monitored until fully recovered to within baseline FEV_1.

5.1.2.2 Potential Effects in Patients with Comorbid Conditions

Bronchial challenge testing with mannitol should be performed with caution in patients with conditions that may increase sensitivity to the bronchoconstriction or other potential effects of mannitol, such as severe cough, ventilatory impairment, spirometry-induced bronchoconstriction, hemoptysis of unknown origin, pneumothorax, recent abdominal or thoracic surgery, recent intraocular surgery, unstable angina, or active upper or lower respiratory tract infection.

5.1.3 Management of Patients Who Experience Specific Adverse Events

5.1.3.1 Dose Modifications and Treatment Interruption

Dose modification and treatment interruption is not allowed in this study. Guidelines for management of specific adverse events are outlined in Table 4 below.

5.1.3.2 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 4. Additional guidelines are provided in the subsections below. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events

Event	Action to Be Taken
[redacted]	
Coagulation abnormalities	
Grade ≥ 3 PT prolongation (PT ≥ 1.5 × ULN)	• Discontinue study drug.
INR of > 2 and < 4	• Administer Vitamin K (2.5 mg PO × 1). • Repeat coagulation parameters daily until INR improves to < 1.5.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Coagulation abnormalities	
INR ≥4 without evidence of bleeding	• Contact Medical Monitor. • Administer Vitamin K (10 mg PO daily) until INR <1.5 and at least 5 GDC-6599 drug-elimination half-lives have elapsed (estimated to be 4 days). • If no response to Vitamin K, consider administering PCC or FFP. • Consider subspecialist (hematology) consultation.
INR ≥4 and Grade 3 or Grade 4 bleeding	• Discontinue study drug. • Administer 4-factor PCC or FFP.
[redacted]	
Impaired cough reflex	
[redacted]	

FFP = fresh frozen plasma; GGT = gamma-glutamyl transferase; IDSA = Infectious Diseases Society of America; PCC = prothrombin complex concentrate; ULN = upper limit normal; PO = by mouth.

[a] https://www.idsociety.org/practice-guideline/practice-guidelines/#/date_na_dt/DESC/0/+/).

5.1.3.3 Management of Increases in QT Interval

Study drug should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms and > 60 ms longer than the baseline value
- Sustained absolute QTcF that is > 515 ms
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of patients with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such patients.

In rare circumstances, it may be acceptable to resume study drug, at a lower dose, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to DAIDS Table v2.1 toxicity scale; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- [redacted]
- Clinically significant Grade ≥3 adverse event, as determined by the investigator
- [redacted]
  - [redacted]
- [redacted]
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6. The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The investigator will use the DAIDS toxicity grading scale (HHS 2017), with slight modifications for clarity and for alignment with internal practices (see Appendix 10), for assessing the severity of each adverse event reported during the study. The investigator will use the grading scale in Table 5 for assessing the severity of adverse events that are not specifically listed in the DAIDS toxicity grading scale.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in DAIDS Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

DAIDS = Division of AIDS.

Notes: Developed by the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services.

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 6 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.

- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high BP), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).This includes death attributed to progression condition being studied.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of chronic cough, "chronic cough progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Chronic Cough

Medical occurrences or symptoms of deterioration that are anticipated as part of chronic cough should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening of chronic cough on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of chronic cough").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For GDC-6599 (or matching placebo), adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.

- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with GDC-6599 (or matching placebo), regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review PRO data for adverse events.

5.3.5.13 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur $>$28 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within [redacted] after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be

reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within [redacted] after the final dose of study drug. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

In this study, VitaloJAK is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

Although the digital cough counting device is not considered a medical device in this study, the investigator must follow the same reporting procedures for device complaints and adverse events as outlined above.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Section 5.4.3.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), if the event is believed to be related to prior exposure to study drug. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
GDC-6599	GDC-6599 Investigator's Brochure
Mannitol (Aridol®/Osmohale®)	U.K. Summary of Product Characteristics

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of the data from the treatment period will be performed when all patients have either completed two treatment periods (Study Visit 7) or discontinued early from the study.

The analysis of complete data from the study, including data from the treatment periods and the safety follow-up period, will be performed when all patients have either completed the treatment periods and the safety follow-up period or discontinued early from the study, all data from the study are in the database, and the database is locked.

6.1 DETERMINATION OF SAMPLE SIZE

A sample size of *approximately 20 to 30 patients* per cohort *(as specified in Sections 3.1.1 and 4.1)* is expected to provide sufficient data to evaluate the primary objectives.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, weight, BMI, self-reported race/ethnicity) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by cohorts.

6.4 EFFICACY ANALYSES

The purpose of this study is estimation and hypothesis generation regarding efficacy and activity of GDC-6599, as compared with placebo, in patients with CRC with asthma or UCC. The effects of GDC-6599 on cough will also be assessed in a subgroup of patients with CRC with COPD. Statistical summaries will be descriptive in nature (e.g., incidence rates, means, standard deviations, and percentiles). Any patients who received any amount of GDC-6599 or placebo will be included in the analyses. Patients will be grouped according to the treatment received in a given period. Final results will be summarized for GDC-6599 and for the placebo periods. No formal hypothesis testing will be performed.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs. All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to DAIDS toxicity grading scale (see Section 5.3.3 and Appendix 10). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. Relevant laboratory, vital sign (pulse rate, respiratory rate, BP, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with sufficient data to enable estimation of key parameters (e.g., area under the concentration–time curve [AUC], time to maximum concentration [t_{max}], C_{max}, half-life), with patients grouped according to treatment received.

Individual and mean plasma GDC-6599 concentration-versus-time data will be tabulated and plotted. The plasma pharmacokinetics of GDC-6599 may be analyzed via non-compartmental analysis and/or compartmental modeling as appropriate for the data collected.

Additional PK analyses will be conducted as appropriate. Exploratory analyses to assess relationships between plasma concentration or PK parameters of GDC-6599 and PD biomarkers, efficacy and/or activity outcomes, or safety outcomes may be conducted as appropriate.

6.7 BIOMARKER ANALYSES

Although no formal statistical analyses of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

6.8 OPTIONAL INTERIM ANALYSIS

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct interim safety and activity analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed *by the IMC (see Section 3.1.2)*.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data, with the exception of the [redacted] which will be collected in paper format. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, medication inventory records, and images, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, patient to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for

Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety related- communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, *data may be disseminated as described in* Section 9.5 .

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 18 sites globally will participate to enroll approximately 80 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.10. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety throughout the study.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/*or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Anderson SD, Perry CP, Brannan JD. Inhaled mannitol in the diagnosis and the management of asthma. Clin Pulm Med 2016;23:258–64.

Arne M, Emtner M, Janson S, et al. COPD patients' perspectives at the time of diagnosis: a qualitative study. Prim Care Respir J 2007;16:215–21.

Backer V, Klein DK, Bodtger U, et al. Clinical characteristics of the BREATHE cohort–a real-life study on patients with asthma and COPD. Eur Clin Respir J 2020;7:1736934.

Balestrini A, Joseph V, Dourado M, et al. A TRPA1 inhibitor suppresses neurogenic inflammation and airway contraction for asthma treatment. J Exp Med 2021;218:e20201637.

Barton A, Gaydecki P, Holt K, et al. Data reduction for cough studies using distribution of audio frequency content. Cough 2012;8:12.

Belvisi MG, Dubuis E, Birrell MA. Transient receptor potential A1 channels: insights into cough and airway inflammatory disease. Chest 2011;140:1040–47.

Belvisi MG, Birrell MA, Khalid S, et al. Neurophenotypes in airway diseases. Insights from translational cough studies. Am J Respir Crit Care Med 2016;193:1364–72.

Belvisi MG, Birrell MA, Wortley MA, et al. XEN-D0501, a novel transient receptor potential vanilloid 1 antagonist, does not reduce cough in patients with refractory cough. Am J Respir Crit Care Med 2017;196:1255–63.

Birrell MA, Belvisi MG, Grace M, et al. TRPA1 agonists evoke coughing in guinea pig and human volunteers. Am J Respir Crit Care Med 2009;180:1042–7.

Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax 2003;58:339–43.

Birring SS, Fleming T, Matos S, et al. The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. Eur Respir J 2008;31:1013–8.

Canning BJ, Chang AB, Bolser DC, et al. Anatomy and neurophysiology of cough: CHEST Guideline and Expert Panel report. Chest 2014;146:1633–48.

Çolak Y, Afzal S, Lange P, et al. Role and impact of chronic cough in individuals with asthma from the general population. J Allergy Clin Immunol Pract 2019;7:1783–92.

Cook NS, Kostikas K, Gruenberger JB, et al. Patients' perspectives on COPD: findings from a social media listening study. ERJ Open Res 2019;5:00128-2018.

de Oliveira JC, de Carvalho Aguiar I, de Oliveira Beloto AC, et al. Clinical significance in COPD patients followed in a real practice. Multidiscip Respir Med 2013;8:43.

Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184:602–15.

Flockhart DA, Thacker D, McDonald C, et al. The Flockhart cytochrome P450 drug–drug interaction table. Division of Clinical Pharmacology, Indiana University School of Medicine [updated 2021; cited 6 February 2022]. Available from: https://drug-interactions.medicine.iu.edu

Gater A, Nelsen L, Fleming S, et al. Assessing asthma symptoms in adolescents and adults: qualitative research supporting development of the asthma daily symptom diary. Value Health 2016;19:440–50.

[GINA] Global Initiative for Asthma. Global strategy for asthma management and prevention [resource on the Internet]. 2016 [cited 6 February 2022]. Available from: http://www.ginasthma.org.

Globe G, Martin M, Schatz M, et al. Symptoms and markers of symptom severity in asthma—content validity of the asthma symptom diary. Health Qual Life Outcomes 2015;13:21.

[GOLD] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2019 report [resource on the Internet] 2019 [cited 10 February 2022]. Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf

Grace MS and Belvisi MG. TRPA1 receptors in cough. Pulm Pharmacol Ther 2011;24:286–8.

Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med 2019;200:e70–88.

Gu Q, Lee LY. Airway irritation and cough evoked by acid: from human to ion channel. Curr Opin Pharmacol 2011;11:238–47.

Hajiro T, Nishimura K, Tsukino M, et al. A comparison of the level of dyspnea vs disease severity in indicating the health-related quality of life of patients with COPD. Chest 1999;116:1632–7.

Hankinson J, Odencrantz J, Fedan B. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179–87.

[HHS] U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, corrected version 2.1 [resource on the Internet]. 2017 [cited: 6 February 2022]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

Hilton EC, Baverel PG, Woodcock A, et al. Pharmacodynamic modeling of cough responses to capsaicin inhalation calls into question the utility of the C5 end point. J Allergy Clin Immunol 2013;132:847–55.

Irwin RS, Richardson ND. Patient-focused care: using the right tools. Chest 2006;130(1 Suppl):73S–82S.

Irwin RS, French CL, Chang AB, et al. Classification of cough as a symptom in adults and management algorithms: CHEST Guideline and Expert Panel Report. Chest 2018;153:196–209.

Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD assessment test. Eur Respir J 2009;34:648–54.

Joseph V, Yang X, Gao SS, et al. Development of AITC-induced dermal blood flow as a translational in vivo biomarker of TRPA1 activity in human and rodent skin. Br J Clin Pharmacol 2021;87:129–39.

Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902–7.

Juniper EF, Svensson K, Mörk AC, et al. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005;99:553–8.

Juniper EF, Bousquet J, Abetz L, et al., for the GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006;100:616–21.

Kanemitsu Y, Fukumitsu K, Kurokawa R, et al. Increased capsaicin sensitivity in patients with severe asthma Is associated with worse clinical outcome. Am J Respir Crit Care Med 2020;201:1068–77.

Kessler R, Partridge MR, Miravitlles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. Eur Respir J 2011;37:264–72.

Khalid S, Murdoch R, Newlands A, et al. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. J Allergy Clin Immunol 2014;134:56–62.

Koskela HO, Hyvärinen L, Brannan JD, et al. Coughing during mannitol challenge is associated with asthma. Chest 2004;125:1985–92.

Koskela HO, Lake C, Wong K, et al. Cough sensitivity to mannitol inhalation challenge identifies subjects with chronic cough. Eur Respir J 2018;51:1800294.

Koskela HO, Nurmi HM, Purokivi MK. Cough-provocation tests with hypertonic aerosols. ERJ Open Res 2020;6:00338-2019.

Koskela HO, Nurmi HM, Birring SS. Utility of cough provocation tests in chronic cough and respiratory diseases: A comprehensive review and introduction of new reference ranges for the capsaicin test. Allergy Asthma Immunol Res 2021;13:833–49.

Leuppi JD, Tandjung R, Anderson SD, et al. Prediction of treatment-response to inhaled corticosteroids by mannitol-challenge test in COPD. A proof of concept. Pulm Pharmacol Ther 2005;18:83–8.

Lipworth BJ, Short PM, Williamson PA, et al. A randomized primary care trial of steroid titration against mannitol in persistent asthma: STAMINA trial. Chest 2012;141:607–15.

Long L, Yao H, Tian J, et al. Heterogeneity of cough hypersensitivity mediated by TRPV1 and TRPA1 in patients with chronic refractory cough. Respir Res 2019;20: 112–20.

Mahler DA, Faryniarz K, Tomlinson D, et al. Impact of dyspnea and physiologic function on general health status in patients with chronic obstructive pulmonary disease. Chest 1992;102:395–401.

Mai Y, Fang L, Zhong S, et al. Methods for assessing cough sensitivity. J Thorac Dis 2020;12:5224–37.

Marsden PA, Satia I, Ibrahim B, et al. Objective cough frequency, airway inflammation, and disease control in asthma. Chest 2016;149:1460–6.

Mazzone SB, Undem BJ. Vagal afferent innervation of the airways in health and disease. Physiol Rev 2016;96:975–1024.

Mincheva R, Ekerljung L, Bjerg A, et al. Frequent cough in unsatisfactory controlled asthma—results from the population-based West Sweden Asthma study. Respir Res 2014;15:79.

Miravitlles M, Worth H, Soler Cataluña JJ, et al. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. Respir Res 2014;15:122.

Morice AH, Fontana GA, Belvisi MG, et al. ERS guidelines on the assessment of cough. Eur Respir J 2007;29:1256–76.

Morice AH, Faruqi S, Wright CE, et al. Cough hypersensitivity syndrome: a distinct clinical entity. Lung 2011;189:73–9.

Morice AH, Millqvist E, Belvisi MG, et al. Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. Eur Respir J 2014;44:1132–48.

Morice AH, Millqvist E, Bieksiene K, et al. European Respiratory Society guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J 2020;55.

Mukhopadhyay I, Kulkarni A, Aranake S, et al. Transient receptor potential ankyrin 1 receptor activation in vitro and in vivo by pro-tussive agents: GRC 17536 as a promising anti-tussive therapeutic. PLoS One 2014;9:e97005.

National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program, Third expert panel on the diagnosis and management of asthma. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. [resource on the Internet] 2007 [cited: 6 February 2022]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7232/.

Niimi A, Matsumoto H, Ueda T, et al. Impaired cough reflex in patients with recurrent pneumonia. Thorax 2003;58:152–3.

Nurmi HM, Lätti AM, Brannan JD, et al. Comparison of mannitol and citric acid cough provocation tests. Respir Med 2019;158:14–20,

Osman LM, McKenzie L, Cairns J, et al. Patient weighting of importance of asthma symptoms. Thorax 2001;56:138–42.

Polley L, Yaman N, Heaney L, et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. Chest 2008;34:295–302.

Quanjer PH, Stanojevic S, Cole TJ, et al., for ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40:1324–43.

Reese RM, Dourado M, Anderson K, et al. Behavioral characterization of a CRISPR-generated TRPA1 knockout rat in models of pain, itch, and asthma. Sci Rep 2020;10:979.

Revicki DA, Leidy NK, Brennan-Diemer F, et al. Integrating patient preferences into health outcomes assessment: the multi-attribute Asthma Symptom Utility Index. Chest 1998;114:998–1007.

Satia I, Tsamandouras N, Holt K, et al. Capsaicin-evoked cough responses in asthmatic patients: evidence for airway neuronal dysfunction. J Allergy Clin Immunol 2017;139:771–9.

Smith JA, Holt K, Dockry R, et al. Performance of a digital signal processing algorithm for the accurate quantification of cough frequency. Eur Respir J 2021;58(2):2004271.

Song WJ, Chang YS, Faruqi S, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. Eur Respir J 2015;45:1479–81.

Song WJ and Morice AH. Cough hypersensitivity syndrome: a few more steps forward. Allergy Asthma Immunol Res 2017;9:394–402.

Sverrild A, Porsbjerg C, Thomsen SF, et al. Diagnostic properties of inhaled mannitol in the diagnosis of asthma: a population study. J Allergy Clin Immunol 2009;124:928–32.

Sverrild A, Hansen S, Hvidtfeldt M, et al. The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM). Eur Respir J 2021;59:2101296.

van der Molen T, Willemse BW, Schokker S, et al. Development, validity and responsiveness of the clinical COPD questionnaire. Health Qual Life Outcomes 2003;1:13.

Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187:347–65.

Yousaf N, Lee KK, Jayaraman B, et al. The assessment of quality of life in acute cough with the Leicester Cough Questionnaire (LCQ-acute). Cough 2011;7:4.

Zhang XF, Chen J, Faltynek CR, et al. Transient receptor potential A1 mediates an osmotically activated ion channel. Eur J Neurosci 2008;27:605–11.

Appendix 1
Schedule of Activities for Part A and Part B

	Scr. [a]	Rand. [a]	Treatment Period 1			WP	Pretreat.	Treatment Period 2			WP	SFU [b]	UV [c]	TD [d]
Study Visit	1	2		3	4		5		6	7		8		
Study Day	–21 to –1													
Informed consent	x [g]													
Review eligibility criteria	x		x											
Demographic data	x													
Medical history and baseline conditions	x													
Weight	x													
Height	x													
Single 12-lead ECG	x		x		x			x		x		x	x	x
Complete physical examination	x											x	x	x
Limited physical examination			x		x			x		x				
Sensory neurologic examination			x		x			x		x		x	x	x
Vital signs	x		x		x			x		x		x	x	x
Hematology	x		x		x			x		x		x	x	x
Chemistry	x		x	x [h]	x			x	x [h]	x		x	x	x
INR, aPTT, PT	x		x		x			x		x		x	x	x
ImmunoCAP™ Specific IgE *test panel, skin prick test, or RAST* [i]	x													

Appendix 1: Schedule of Activities for Part A and Part B

	Scr. [a]	Rand. [a]	Treatment Period 1			WP	Pretreat.	Treatment Period 2			WP	SFU [b]	UV [c]	TD [d]
Study Visit	1	2		3	4		5		6	7		8		
Study Day	–21 to –1													
Vitamin K–dependent coagulation factors			x		x			x		x		x	x	x
Viral serology	x													
FSH (if necessary) [j]	x													
Pregnancy test [k]	x		x					x				x	x	
COVID-19 testing (if necessary) [n]	x													
Chest X-ray (if no historical Chest X-ray or HRCT) [o]	x													
VAS [q]	x [r]	Daily [r]					Daily [r]					x		x
NRS	x [r]	Daily [r]					Daily [r]					x		x
FeNO			x		x			x		x				
Pre-bronchodilator spirometry [s]	*x*		*x*		*x*		*x*	*x*		*x*				

Appendix 1: Schedule of Activities for Part A and Part B

	Scr. [a]	Rand. [a]	Treatment Period 1			WP	Pretreat.	Treatment Period 2			WP	SFU [b]	UV [c]	TD [d]
Study Visit	1	2		3	4		5		6	7		8		
Study Day	–*21* to –1	[redacted]												
Mannitol challenge test [t]	x				x *(Optional)*					x *(Optional)*				
Post-bronchodilator spirometry [s]	x [u]													
24-hour OCC (VitaloJAK®) [v]	x [w]	x [x]	x [y]		x [y]		x [x]	x [y]		x [y]				
[redacted]														
Randomization		x												
Study drug administration (GDC-6599 or placebo)			[redacted] on Days 1–14 [aa]					[redacted] on Days *30–43* [aa]						
Patient-reported daily compliance eDiary			Daily					Daily						

Appendix 1: Schedule of Activities for Part A and Part B

	Scr. [a]	Rand. [a]	Treatment Period 1			WP	Pretreat.	Treatment Period 2			WP	SFU [b]	UV [c]	TD [d]
Study Visit	1	2		3	4		5		6	7		8		
Study Day	–21 to –1	[redacted]												
Concomitant medications	x	x	x	x	x		x	x	x	x		x	x	x
Adverse events [dd]	x	x	x	x	x		x	x	x	x		x	x	x

[redacted] *ATS = American Thoracic Society;* [redacted] COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; CRC = chronic refractory cough; eDiary = electronic diary; *ERS = European Respiratory Society;* $FeNO$ = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second: FSH = follicle-stimulating hormone; *FVC = forced vital capacity;* [redacted] HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HRCT = high-resolution computed tomography; [redacted] NRS = Numeric Response Scale; OCC = objective cough count; PK = pharmacokinetic; Pretreat. = pretreatment; PRO = patient-reported outcome; Rand. = randomization; *RAST = radioallergosorbent test;* RBR = Research Biosample Repository; Scr. = screening; SFU = safety follow-up; TD = treatment discontinuation; ULN = upper limit of normal; UCC = unexplained chronic cough; UV = unscheduled visit; VAS = visual analog scale; WES = whole exome sequencing; WGS = whole genome sequencing; WP = washout period .

Notes: On days *with in-clinic dosing*, all assessments should be performed prior to *study drug administration*, unless otherwise specified.

Appendix 1: Schedule of Activities for Part A and Part B

[a] Results of standard-of-care assessments performed prior to obtaining informed consent and within 21 days prior to Day 1 may be used; such assessments do not need to be repeated for screening. Patients who do not meet the criteria for participation in this study may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion, as described in Section 3.1.1. If a patient has completed all screening assessments and is eligible to enroll, randomization of the patient may begin as soon as 7 days into the screening period. *The screening visit may occur during a single day or over a maximum of 3 days. If performed during a single screening visit, use of the VitaloJAK cough recorder should start at least 30 minutes after the mannitol challenge test.*

[b] Patients who complete both treatment periods will return to the clinic for a safety follow-up visit (Study Visit 8) at [redacted].

[c] Visit not specified by the protocol. Assessments (possibly including PK and biomarker sample collection; see [redacted] should be performed as clinically indicated. Suggested safety assessments are outlined in this appendix table.

[d] Patients who discontinue study drug prematurely will return to the clinic for a treatment discontinuation [redacted] days after their final dose of study drug.

[redacted]

[g] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than *21 days* before initiation of study treatment.

[h] Chemistry panel limited to liver function tests (ALP, ALT, AST, total and direct bilirubin). If finding of an elevated ALT/AST ($>3\times$ULN and $<5\times$ULN) and no other findings consistent with Hy's Law are observed, continue study drug and return to clinic for and unscheduled visit to repeat liver function tests (ALT, AST, GGT, alkaline phosphatase, total and direct bilirubin) within 48 hours.

If finding of an elevated ALT/AST $\geq 5\times$ULN in isolation or $>3\times$ULN in combination with other findings consistent with Hy's Law are observed, discontinue study drug, repeat liver function test within 72 hours, assess patient for signs/symptoms of hepatic failure, assess for other causes of liver dysfunction (e.g., viral hepatitis, concomitant medications, etc.), and continue to monitor liver function tests until abnormalities resolve (see Section 5.1.3.2).

For patients at participating sites who have provided written informed consent to participate in mobile nursing visits, these assessments may be performed by a trained nursing professional at the patient's home or another suitable location, if mobile nursing is available.

[i] The ImmunoCAP *Specific IgE* test panel*, skin prick test, or RAST* is required *only* **for patients with asthma who do not have confirmed atopic versus non-atopic status in their medical records**. Patient eligibility may be determined by medical history alone (see Section 4.1.1.2).

[j] Test for FSH may be performed at screening to confirm postmenopausal state, if required per local guidelines.

[k] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. On days when both pregnancy test and study drug administration are scheduled, the pregnancy test results must be available prior to dosing.

[l] [redacted]

[m] *Urine sample for urinalysis only. Leftover urine sample should not be collected for urine creatinine or biomarkers.*

[n] COVID-19 testing to be performed as per local regulations or institutional policies.

[o] Chest X-ray is to be performed in the following instances:

Patients with CRC with asthma or UCC: if no scans have been completed within the last 5 years prior to screening.

Patients with CRC with COPD: if no scans have been completed within the last 6 months prior to screening.

[p] [redacted]

[q] On days when multiple PRO assessments are scheduled, the order of questionnaire completion is the following: [redacted], VAS, and NRS. [redacted]

[r] *VAS will be self-administered once at screening visit via an electronic device at the study site.* VAS and NRS will be self-administered daily *in the evening* during the remainder of screening and treatment periods using a take-home electronic device.

[s] *The patient is to perform a minimum of three acceptable FVC maneuvers according to the ATS/ERS 2019 guidelines (Graham et al. 2019). The difference between two largest acceptable FVC and FEV_1 measurements must be within 0.15 L (150 mL) variability to meet the repeatability criteria. If there is greater than 0.15 L variability between the three readings, the patient is to perform another FEV_1 measurement.* Details on spirometry are provided in Section 4.5.7 and in the pulmonary function and cough monitoring guidance *documents. For the screening visits, pre-bronchodilator spirometry should be performed immediately prior to initiating the mannitol challenge test to determine the pre-challenge FEV_1 % predicted value. For subsequent study visits, pre-bronchodilator spirometry should be performed immediately prior to initiating the mannitol challenge test if optional mannitol challenge tests are performed, or should be performed at least 2.5 hours following drug administration.*

[t] Details on the mannitol challenge test are provided in Section 4.5.5 and in the mannitol challenge test guidance. Medication restrictions prior to the mannitol challenge are provided in Section 4.4.4). *If the optional mannitol challenge test is performed at Visit 4 and/or 7, it is to be performed at least 2.5 hours after study drug administration.*

[u] Post-bronchodilator spirometry replaces the recovery spirometry assessment *[if required]* following mannitol challenge at screening. Post-bronchodilator spirometry should be performed per the pulmonary function and cough monitoring guidance *documents* at least 1 hour following the mannitol challenge test or on a separate study visit within the screening period before or after the mannitol challenge test.

[v] Details on cough monitoring are provided in Section 4.5.6 and in the pulmonary function and cough monitoring guidance *documents*.

[w] *Cough monitoring with the VitaloJAK cough recorder will begin on the first day of screening and will continue for 24 hours if the screening visits occur over multiple visits. If screening visit occurs during a single visit, use of the VitaloJAK cough recorder should start at least 30 minutes after the mannitol challenge test.*

[x] Cough monitoring with the VitaloJAK cough recorder will begin a minimum of 24 hours prior to study drug administration and will conclude on the day of study drug administration.

[y] Cough monitoring with the VitaloJAK cough recorder will begin at the *end* of the mannitol challenge test *(i.e., immediately after spirometry following the last dose of mannitol or after the final spirometry following the recovery period [if required])* and will continue for 24 hours after mannitol challenge recovery period. *If the mannitol challenge test is not performed, cough monitoring with the VitaloJAK cough recorder will begin approximately 3 hours after study drug administration.*

[z] [redacted]

[aa] Study drug (GDC-6599 or placebo) will be administered on Days 1–14 and on Days *30–43*. [redacted]

[bb] [redacted]

[cc] [redacted]

[dd] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug.

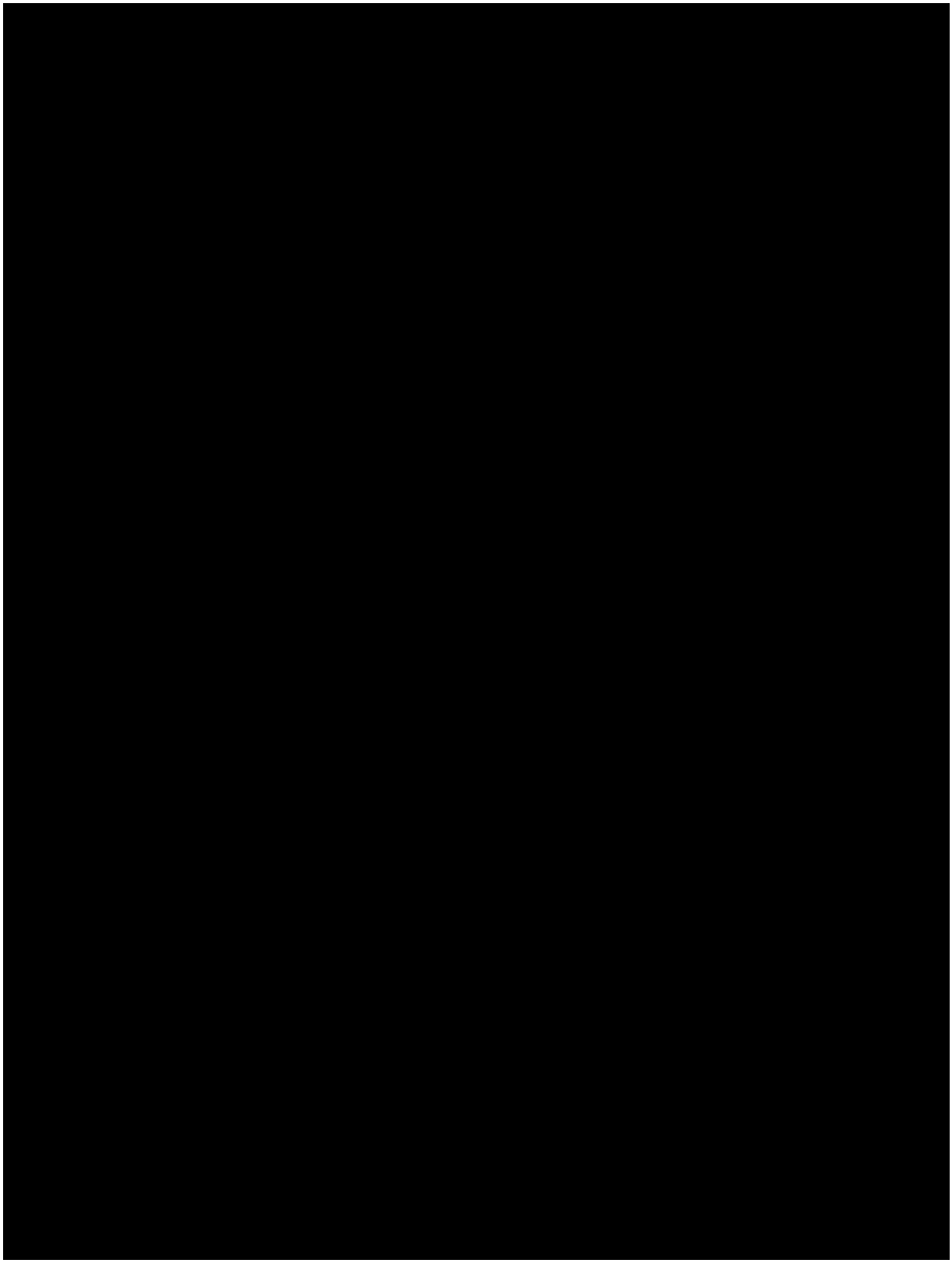
Reference:

Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med 2019;200:e70–88.

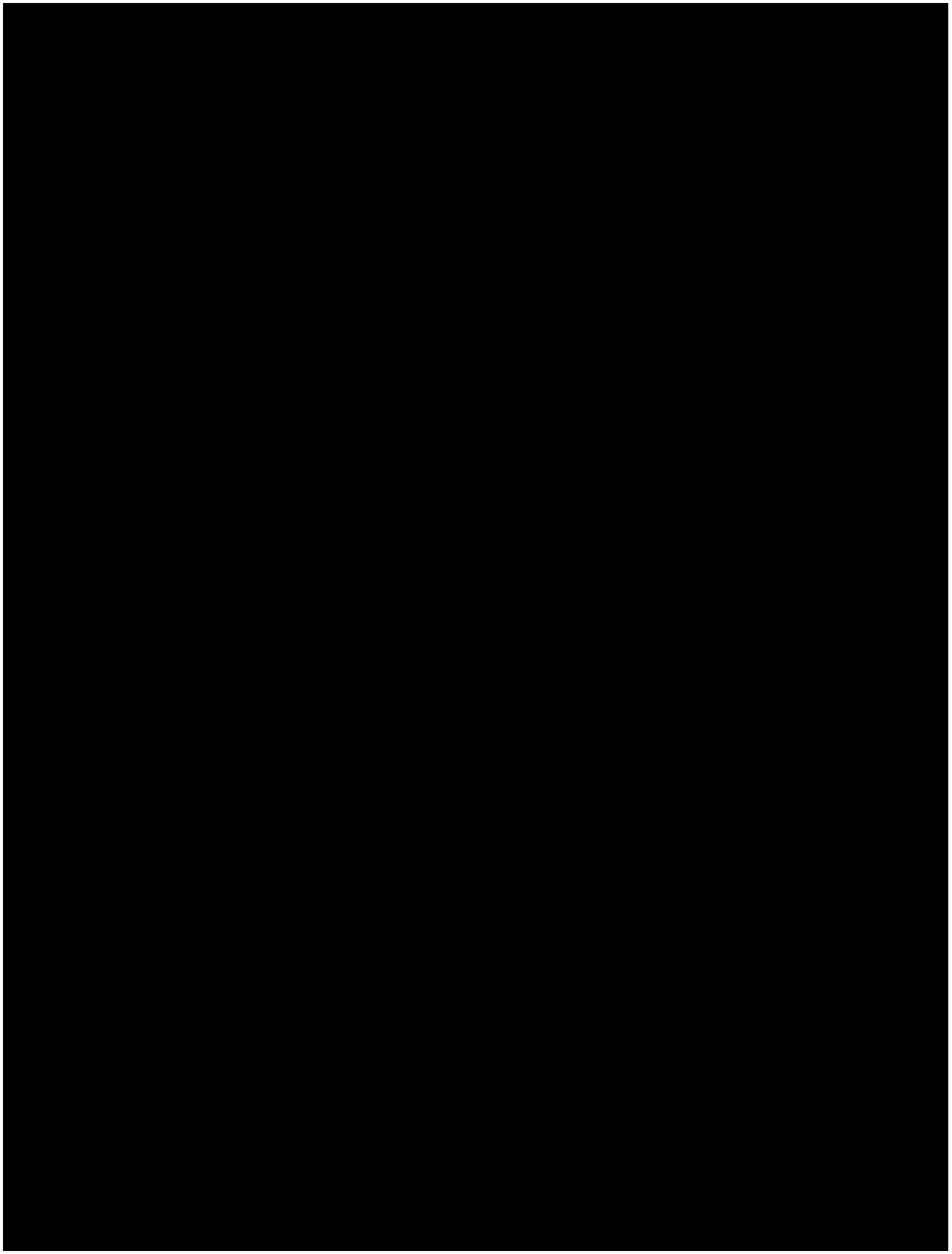
[redacted]

[redacted]

[redacted]



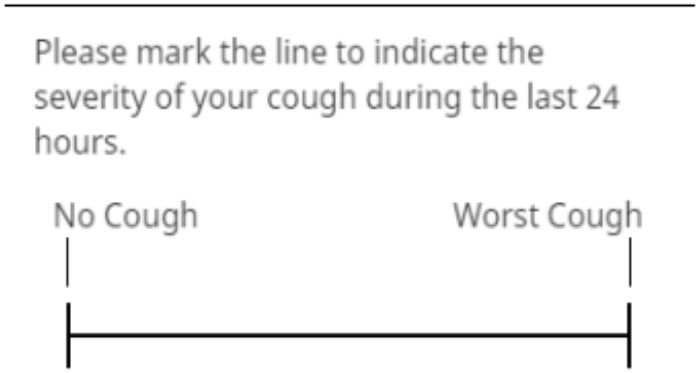
[redacted]



[redacted]

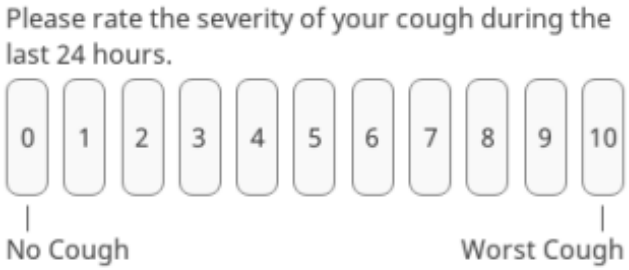
Appendix 6
Visual Analog Scale

<u>Do not reproduce or distribute</u>. The Sponsor will provide sites with all instruments to be completed in this study.



Appendix 7
Numeric Response Scale

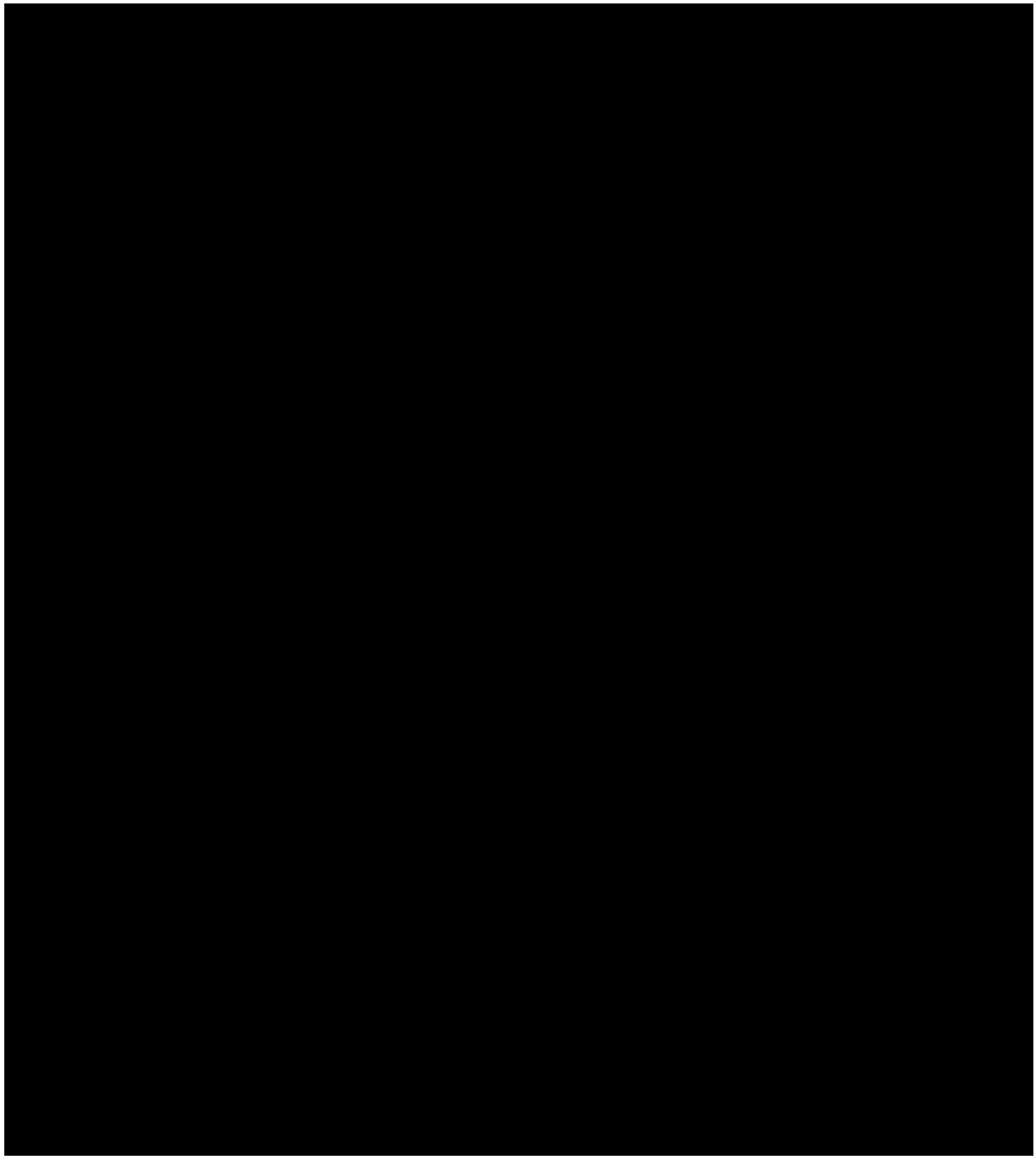
<u>Do not reproduce or distribute</u>. The Sponsor will provide sites with all instruments to be completed in this study.



[redacted]

[redacted]

[redacted]



Appendix *9*
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix *10*
Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

The investigator will use the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (HHS 2017), with slight modifications for clarity and for alignment with internal practices, for assessing the severity of each adverse event reported during the study.

Table 1 Severity Grading for Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Cardiovascular				
Arrhythmia (by ECG or physical examination) (Specify type if applicable)	No symptoms and no intervention indicated	No symptoms and non-urgent intervention indicated	Non–life-threatening symptoms and non-urgent intervention indicated	Life-threatening arrhythmia or urgent intervention indicated
Hypertension (with the lowest reading taken after repeat testing during a visit): ≥ 18 years of age	140 to < 160 mmHg systolic or 90 to < 100 mmHg diastolic [a]	≥ 160 to < 180 mmHg systolic or ≥ 100 to < 110 mmHg diastolic [a]	≥ 180 mmHg systolic or ≥ 110 mmHg diastolic [a]	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) or hospitalization indicated
Hypertension (with the lowest reading taken after repeat testing during a visit): < 18 years of age [b]	> 120 mmHg systolic or > 80 mmHg diastolic, but systolic and diastolic < 95th percentile adjusted for age, height, and sex	≥ 95th to < 5 mmHg above the 99th percentile adjusted for age, height, and sex (systolic and/or diastolic) [a]	≥ 5 mmHg above the 99th percentile adjusted for age, height, and sex (systolic and/or diastolic) [a]	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) or hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms and IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

[a] When systolic and diastolic blood pressures meet criteria for different grades, the higher grade should be used.

[b] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011;128(Suppl 5):S213–56.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Cardiovascular (cont.)				
Cardiac ischemia or infarction (Report the most appropriate term)	—	—	New symptoms with ischemia (stable angina) or new testing consistent with ischemia	Unstable angina or acute myocardial infarction
Heart failure	No symptoms and laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) or intervention indicated (e.g., oxygen)	Life-threatening consequences or urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	—	Symptoms and no transfusion indicated	Symptoms and transfusion of ≤2 units packed RBCs (for children, packed RBCs ≤10 cc/kg) indicated	Life-threatening hypotension or transfusion of >2 units packed RBCs (for children, packed RBCs >10 cc/kg) indicated
Prolonged PR interval or AV block: >16 years of age (Report the most appropriate term)	PR interval 0.21 to <0.25 seconds	PR interval ≥0.25 seconds or Type I second-degree AV block	Type II second-degree AV block or ventricular pause ≥3.0 seconds	Complete AV block
Prolonged PR interval or AV block: ≤16 years of age (Report the most appropriate term)	First-degree AV block (PR interval >normal for age and rate)	Type I second-degree AV block	Type II second-degree AV block or ventricular pause ≥3.0 seconds	Complete AV block
Prolonged QTc interval (corrected per Bazett's formula)	0.45 to 0.47 seconds	>0.47 to 0.50 seconds	>0.50 seconds or ≥0.06 seconds above baseline	Life-threatening consequences (e.g., torsade de pointes, other associated serious ventricular dysrhythmia)

AV = atrioventricular.

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Cardiovascular (cont.)				
Thrombosis or embolism (Report the most appropriate term)	—	Symptoms and no intervention indicated	Symptoms and intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
Dermatologic				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing greater than minimal interference with usual social and functional activities	—	—
Bruising	Localized to one area	Localized to more than one area	Generalized	—
Cellulitis	—	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social and functional activities	Marked or generalized causing greater than minimal interference with usual social and functional activities	—	—
Hypopigmentation	Slight or localized causing no or minimal interference with usual social and functional activities	Marked or generalized causing greater than minimal interference with usual social and functional activities	—	—

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Dermatologic (cont.)				
Petechiae	Localized to one area	Localized to more than one area	Generalized	—
Pruritus [c] (without skin lesions)	Itching causing no or minimal interference with usual social and functional activities	Itching causing greater than minimal interference with usual social and functional activities	Itching causing inability to perform usual social and functional activities	—
Rash (Specify type, if applicable)	Localized rash	Diffuse rash or target lesions	Diffuse rash and vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions or ulceration of mucous membrane involving two or more distinct mucosal sites or Stevens-Johnson syndrome or toxic epidermal necrolysis
Endocrine and Metabolic				
Diabetes mellitus	Controlled without medication	Controlled with medication or modification of current medication regimen	Uncontrolled despite treatment modification or hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing pain with greater than minimal interference with usual social and functional activities	Disfiguring changes and symptoms requiring intervention or causing inability to perform usual social and functional activities	—

[c] For pruritus associated with injections or infusions, see "Site Reactions to Injections and Infusions"

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Endocrine and Metabolic (cont.)				
Hyperthyroidism	No symptoms and abnormal laboratory value	Symptoms causing greater than minimal interference with usual social and functional activities or thyroid suppression therapy indicated	Symptoms causing inability to perform usual social and functional activities or uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms and abnormal laboratory value	Symptoms causing greater than minimal interference with usual social and functional activities or thyroid replacement therapy indicated	Symptoms causing inability to perform usual social and functional activities or uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (disorder characterized by fat loss in the face, extremities, and buttocks)	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing greater than minimal interference with usual social and functional activities	Disfiguring changes	—
Lipohypertrophy (disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen)	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing greater than minimal interference with usual social and functional activities	Disfiguring changes	—

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Gastrointestinal				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences or aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms and intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or distension (Report the most appropriate term)	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	—
Cholecystitis	—	Symptoms and medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	—	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea: ≥1 year of age	Transient or intermittent episodes of unformed stools or increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools or increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools over baseline per 24-hour period or IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Gastrointestinal (cont.)				
Diarrhea: < 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools or mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or odynophagia (Report the most appropriate term and specify location)	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or stomatitis (Report the most appropriate term and specify location)	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations or mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) or tissue necrosis or diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent nausea and no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours or rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	—	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Gastrointestinal (cont.)				
Perforation (colon or rectum)	—	—	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social and functional activities or medical intervention indicated	Symptoms causing inability to perform usual social and functional activities or operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal discharge	Visible discharge	Discharge requiring the use of pads	—	—
Vomiting	Transient or intermittent vomiting and no or minimal interference with oral intake	Frequent vomiting episodes and no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension or aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Musculoskeletal				
Arthralgia	Joint pain causing no or minimal interference with usual social and functional activities	Joint pain causing greater than minimal interference with usual social and functional activities	Joint pain causing inability to perform usual social and functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Joint stiffness or swelling causing no or minimal interference with usual social and functional activities	Joint stiffness or swelling causing greater than minimal interference with usual social and functional activities	Joint stiffness or swelling causing inability to perform usual social and functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Musculoskeletal (cont.)				
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social and functional activities	Muscle pain causing greater than minimal interference with usual social and functional activities	Muscle pain causing inability to perform usual social and functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	—	No symptoms but with radiographic findings and no operative intervention indicated	Bone pain with radiographic findings or operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia: ≥ 30 years of age	BMD t-score −2.5 to −1	—	—	—
Osteopenia: < 30 years of age	BMD z-score −2 to −1	—	—	—
Osteoporosis: ≥ 30 years of age	—	BMD t-score < −2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Osteoporosis: < 30 years of age	—	BMD z-score < −2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

BMD = bone mineral density.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neurologic				
Acute CNS ischemia	—	—	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered mental status (for dementia, see cognitive, behavioral, or attentional disturbance below)	Changes causing no or minimal interference with usual social and functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social and functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities	Delirium or obtundation or coma
Ataxia	Symptoms causing no or minimal interference with usual social and functional activities or no symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, behavioral, or attentional disturbance (includes dementia and attention deficit disorder) (Specify type, if applicable)	Disability causing no or minimal interference with usual social and functional activities or specialized resources not indicated	Disability causing greater than minimal interference with usual social and functional activities or specialized resources on part-time basis indicated	Disability causing inability to perform usual social and functional activities or specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions or institutionalization indicated

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neurologic (cont.)				
Developmental delay < 18 years of age (Specify type, if applicable)	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions or hospitalization indicated or headache with significant impairment of alertness or other neurologic function
Neuromuscular weakness (includes myopathy and neuropathy) (Specify type, if applicable)	Minimal muscle weakness causing no or minimal interference with usual social and functional activities or no symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social and functional activities	Muscle weakness causing inability to perform usual social and functional activities	Disabling muscle weakness causing inability to perform basic self-care functions or respiratory muscle weakness impairing ventilation

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neurologic (cont.)				
Neurosensory alteration (includes paresthesia and painful neuropathy) (Specify type, if applicable)	Minimal paresthesia causing no or minimal interference with usual social and functional activities or no symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure, new onset: ≥ 18 years of age	—	—	1–3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) or difficult to control (e.g., refractory epilepsy)
Seizure, new onset: < 18 years of age (includes new or preexisting febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes or ≥ 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) or difficult to control (e.g., refractory epilepsy)
Seizure, preexisting (excludes preexisting febrile seizures)	—	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) or difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness and hospitalization or intervention required	—
Pregnancy, Puerperium, and Perinatal				
Stillbirth	—	—	Fetal death occurring at ≥ 20 weeks gestational age	—

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Pregnancy, Puerperium, and Perinatal (cont.)				
Preterm birth	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous abortion (a pregnancy loss occurring at < 20 weeks gestational age; also known as miscarriage)	Chemical pregnancy	Uncomplicated spontaneous abortion	Complicated spontaneous abortion	—
Psychiatric				
Insomnia	Mild difficulty falling asleep or staying asleep or mild difficulty caused by early morning awakening, causing no or minimal interference with usual social and functional activities	Moderate difficulty falling asleep or staying asleep, or moderate difficulty caused by early morning awakening, causing greater than minimal interference with usual social and functional activities	Severe difficulty falling asleep or staying asleep or severe difficulty caused by early morning awakening, causing inability to perform usual social and functional activities and requiring intervention or hospitalization	—
Psychiatric disorder (includes anxiety, depression, mania, and psychosis) (Specify disorder)	Symptoms with intervention not indicated or behavior causing no or minimal interference with usual social and functional activities	Symptoms with intervention indicated or behavior causing greater than minimal interference with usual social and functional activities	Symptoms with hospitalization indicated or behavior causing inability to perform usual social and functional activities	Threatens harm to self or others or acute psychosis or behavior causing inability to perform basic self-care functions

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Psychiatric (cont.)				
Suicidal ideation or suicide attempt (Report the most appropriate term)	Preoccupied with thoughts of death and no wish to kill oneself	Preoccupied with thoughts of death and wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so or hospitalization indicated	Suicide attempted
Respiratory				
Acute bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥70 to <80% of predicted or mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50% to <70% of predicted or symptoms with intervention indicated or symptoms causing greater than minimal interference with usual social and functional activities	Forced expiratory volume in 1 second or peak flow 25% to <50% of predicted or symptoms causing inability to perform usual social and functional activities	Forced expiratory volume in 1 second or peak flow <25% of predicted or life-threatening respiratory or hemodynamic compromise or intubation
Dyspnea or respiratory distress (Report the most appropriate term)	Dyspnea on exertion with no or minimal interference with usual social and functional activities or wheezing or minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social and functional activities or nasal flaring or intercostal retractions or pulse oximetry 90% to <95%	Dyspnea at rest causing inability to perform usual social and functional activities or pulse oximetry <90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure.

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Sensory				
Hearing loss (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram): ≥ 12 years of age	—	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) or non-serviceable hearing (i.e., > 50 dB audiogram and < 50% speech discrimination)
Hearing loss (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram): < 12 years of age	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) or hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language–related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social and functional activities and intervention not indicated	Symptoms causing greater than minimal interference with usual social and functional activities or intervention indicated	Symptoms causing inability to perform usual social and functional activities	—
Uveitis	No symptoms and detectable uveitis on examination	Anterior uveitis with symptoms or medical intervention indicated	Posterior uveitis or panuveitis or operative intervention indicated	Uveitis with disabling visual loss in affected eye(s)

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Sensory (cont.)				
Vertigo	Vertigo causing no or minimal interference with usual social and functional activities	Vertigo causing greater than minimal interference with usual social and functional activities	Vertigo causing inability to perform usual social and functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social and functional activities	Visual changes causing greater than minimal interference with usual social and functional activities	Visual changes causing inability to perform usual social and functional activities	Visual changes with disabling visual loss in affected eye(s)
Systemic				
Acute allergic reaction	Localized urticaria (wheals) with no intervention indicated	Localized urticaria with intervention indicated or mild angioedema with no intervention indicated	Generalized urticaria or angioedema with intervention indicated or symptoms of mild bronchospasm	Acute anaphylaxis or life-threatening bronchospasm or laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	—

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Systemic (cont.)				
Cytokine-release syndrome (disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath)	Mild signs and symptoms and therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated and responds promptly to symptomatic treatment or prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms or recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or malaise (Report the most appropriate term)	Symptoms of fatigue or malaise causing no or minimal interference with usual social and functional activities	Symptoms of fatigue or malaise causing greater than minimal interference with usual social and functional activities	Symptoms of fatigue or malaise causing inability to perform usual social and functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to <38.6°C or 100.4 to <101.5°F	≥38.6 to <39.3°C or ≥101.5 to <102.7°F	≥39.3 to <40.0°C or ≥102.7 to <104.0°F	≥40.0°C or ≥104.0°F
Pain (not associated with study agent injections and not specified elsewhere) (Specify location)	Pain causing no or minimal interference with usual social and functional activities	Pain causing greater than minimal interference with usual social and functional activities	Pain causing inability to perform usual social and functional activities	Disabling pain causing inability to perform basic self-care functions or hospitalization indicated
Serum sickness (disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea)	Mild signs and symptoms	Moderate signs and symptoms and intervention indicated (e.g., antihistamines)	Severe signs and symptoms and higher level intervention indicated (e.g., corticosteroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Systemic (cont.)				
Underweight: > 5 to 19 years of age	WHO BMI z-score [d] < −1 to −2	WHO BMI z-score [d] < −2 to −3	WHO BMI z-score [d] < −3	WHO BMI z-score [d] < −3 with life-threatening consequences
Underweight: 2 to 5 years of age	WHO weight-for-height z-score [e] < −1 to −2	WHO weight-for-height z-score [e] < −2 to −3	WHO weight-for-height z-score [e] < −3	WHO weight-for-height z-score [e] < −3 with life-threatening consequences
Underweight: < 2 years of age	WHO weight-for-length z-score [e] < −1 to −2	WHO weight-for-length z-score [e] < −2 to −3	WHO weight-for-length z-score [e] < −3	WHO weight-for-length z-score [e] < −3 with life-threatening consequences
Unintentional weight loss (excludes postpartum weight loss)	—	5% to < 9% loss in body weight from baseline	≥ 9% to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline or aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Urinary				
Urinary tract obstruction	—	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

BMI = body mass index; WHO = World Health Organization.

[d] WHO reference tables for participants > 5 to 19 years of age: http://www.who.int/growthref/who2007_bmi_for_age/en/.

[e] WHO reference tables for participants ≤ 5 years of age: http://www.who.int/childgrowth/standards/chart_catalogue/en/.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Site Reactions to Injections and Infusions [f]				
Injection-site pain or tenderness [f]	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social and functional activities	Pain or tenderness causing inability to perform basic self-care function or hospitalization indicated
Injection-site erythema, redness, induration, or swelling: [f] >15 years of age (Report the most appropriate term; report multiple events if appropriate)	2.5 to <5 cm in diameter or 6.25 to <25 cm^2 surface area [g] and symptoms causing no or minimal interference with usual social and functional activities	≥5 to <10 cm in diameter or ≥25 to <100 cm^2 surface area [g] or symptoms causing greater than minimal interference with usual social and functional activities	≥10 cm in diameter or ≥100 cm^2 surface area [g] or ulceration or secondary infection or phlebitis or sterile abscess or drainage or symptoms causing inability to perform usual social and functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection-site erythema, redness, induration, or swelling: [f] ≤15 years of age (Report the most appropriate term; report multiple events if appropriate)	≤2.5 cm in diameter [g]	>2.5 cm in diameter with <50% surface area [g] of the extremity segment involved (e.g., upper arm or thigh)	≥50% surface area [g] of the extremity segment involved (e.g., upper arm or thigh) or ulceration or secondary infection or phlebitis or sterile abscess or drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

[f] Refer to Section 5.3.5.1 for instructions on reporting injection-site reactions to study treatment (if applicable). For reactions to drugs other than study treatment, report the most appropriate term and report multiple events, if applicable.

[g] Grading should be based on the greatest single diameter or measured surface area.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Site Reactions to Injections and Infusions (cont.) [f]				
Injection-site pruritus [f]	Itching localized to the injection site that is relieved spontaneously or requires treatment for < 48 hours	Itching beyond the injection site that is not generalized or itching localized to the injection site that requires treatment for ≥ 48 hours	Generalized itching causing inability to perform usual social and functional activities	—
Chemistries				
Acidosis	—	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, low	3.0 g/dL to < LLN (30 g/L to < LLN)	≥ 2.0 to < 3.0 g/dL (≥ 20 to < 30 g/L)	< 2.0 g/dL (< 20 g/L)	—
Alkaline phosphatase, high	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Alkalosis	—	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, high (Report the most appropriate term)	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Amylase (pancreatic) or amylase (total), high (Report the most appropriate term)	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN

LLN = lower limit of normal; ULN = upper limit of normal.

[f] Refer to Section 5.3.5.1 for instructions on reporting injection-site reactions to study treatment (if applicable). For reactions to drugs other than study treatment, report the most appropriate term and report multiple events, if applicable.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
AST or SGOT, high (Report the most appropriate term)	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Bicarbonate, low	16.0 mEq/L to < LLN (16.0 mmol/L to < LLN)	11.0 to < 16.0 mEq/L (11.0 to < 16.0 mmol/L)	8.0 to < 11.0 mEq/L (8.0 to < 11.0 mmol/L)	< 8.0 mEq/L (< 8.0 mmol/L)
Bilirubin (direct), high: > 28 days of age	—	—	> ULN with other signs and symptoms of hepatotoxicity	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Bilirubin (direct), high: ≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL [h]	> 2 mg/dL [h]
Bilirubin (total), high: > 28 days of age	1.1 to < 1.6 × ULN	1.6 to < 2.6 × ULN	2.6 to < 5.0 × ULN	≥ 5.0 × ULN
Bilirubin (total), high: ≤ 28 days of age	See Table 7			
Calcium, high: ≥ 7 days of age	10.6 to < 11.5 mg/dL (2.65 to < 2.88 mmol/L)	11.5 to < 12.5 mg/dL (2.88 to < 3.13 mmol/L)	12.5 to < 13.5 mg/dL (3.13 to < 3.38 mmol/L)	≥ 13.5 mg/dL (≥ 3.38 mmol/L)
Calcium, high: < 7 days of age	11.5 to < 12.4 mg/dL (2.88 to < 3.10 mmol/L)	12.4 to < 12.9 mg/dL (3.10 to < 3.23 mmol/L)	12.9 to < 13.5 mg/dL (3.23 to < 3.38 mmol/L)	≥ 13.5 mg/dL (≥ 3.38 mmol/L)
Calcium (ionized), high	> ULN to < 6.0 mg/dL (> ULN to < 1.5 mmol/L)	6.0 to < 6.4 mg/dL (1.5 to < 1.6 mmol/L)	6.4 to < 7.2 mg/dL (1.6 to < 1.8 mmol/L)	≥ 7.2 mg/dL (≥ 1.8 mmol/L)

LLN = lower limit of normal; ULN = upper limit of normal.

[h] Direct bilirubin > 1.5 mg/dL in a participant ≤ 28 days of age should be graded as Grade 2, if < 10% of the total bilirubin.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
Calcium, low: ≥7 days of age	7.8 to <8.4 mg/dL (1.95 to <2.10 mmol/L)	7.0 to <7.8 mg/dL (1.75 to <1.95 mmol/L)	6.1 to <7.0 mg/dL (1.53 to <1.75 mmol/L)	<6.1 mg/dL (<1.53 mmol/L)
Calcium, low: <7 days of age	6.5 to <7.5 mg/dL (1.63 to <1.88 mmol/L)	6.0 to <6.5 mg/dL (1.50 to <1.63 mmol/L)	5.50 to <6.0 mg/dL (1.38 to <1.50 mmol/L)	<5.50 mg/dL (<1.38 mmol/L)
Calcium (ionized), low	<LLN to 4.0 mg/dL (<LLN to 1.0 mmol/L)	3.6 to <4.0 mg/dL (0.9 to <1.0 mmol/L)	3.2 to <3.6 mg/dL (0.8 to <0.9 mmol/L)	<3.2 mg/dL (<0.8 mmol/L)
Cardiac troponin I, high	—	—	—	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine kinase, high	3 to <6 × ULN	6 to <10 × ULN	10 to <20 × ULN	≥20 × ULN
Creatinine, high	1.1 to 1.3 × ULN	>1.3 to 1.8 × ULN or increase to 1.3 to <1.5 × baseline [i]	>1.8 to <3.5 × ULN or increase to 1.5 to <2.0 × baseline [i]	≥3.5 × ULN or increase to ≥2.0 × baseline [i]
Creatinine clearance or eGFR, low (Report the most appropriate term)	—	<90 to 60 mL/min or mL/min/1.73 m^2 or 10% to <30% decrease from baseline [j]	<60 to 30 mL/min or mL/min/1.73 m^2 or 30% to <50% decrease from baseline [j]	<30 mL/min or mL/min/1.73 m^2 or ≥50% decrease from baseline [j] or dialysis needed

eGFR = estimated glomerular filtration rate; LLN = lower limit of normal; ULN = upper limit of normal.

[i] For participant with normal baseline value, grade should be based on current value relative to ULN. For participant with elevated baseline value, grade should be based on current value relative to baseline value.

[j] For participant with normal baseline value, grade should be based on current value. For participant with elevated baseline value, grade should be based on current value relative to baseline value.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
Glucose (fasting), high	110 to 125 mg/dL (6.11 to < 6.95 mmol/L)	> 125 to 250 mg/dL (6.95 to < 13.89 mmol/L)	> 250 to 500 mg/dL (13.89 to < 27.75 mmol/L)	≥ 500 mg/dL (≥ 27.75 mmol/L)
Glucose (non-fasting), high	116 to 160 mg/dL (6.44 to < 8.89 mmol/L)	> 160 to 250 mg/dL (8.89 to < 13.89 mmol/L)	> 250 to 500 mg/dL (13.89 to < 27.75 mmol/L)	≥ 500 mg/dL (≥ 27.75 mmol/L)
Glucose, low: ≥28 days of age	55 to 64 mg/dL (3.05 to < 3.55 mmol/L)	40 to < 55 mg/dL (2.22 to < 3.05 mmol/L)	30 to < 40 mg/dL (1.67 to < 2.22 mmol/L)	< 30 mg/dL (< 1.67 mmol/L)
Glucose, low: < 28 days of age	50 to 54 mg/dL (2.78 to < 3.00 mmol/L)	40 to < 50 mg/dL (2.22 to < 2.78 mmol/L)	30 to < 40 mg/dL (1.67 to < 2.22 mmol/L)	< 30 mg/dL (< 1.67 mmol/L)
Lactate, high	ULN to < 2.0 × ULN without acidosis	≥ 2.0 × ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, high	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN
Lipid disorder: cholesterol (fasting), high: ≥ 18 years of age	200 to < 240 mg/dL (5.18 to < 6.19 mmol/L)	240 to < 300 mg/dL (6.19 to < 7.77 mmol/L)	≥ 300 mg/dL (≥ 7.77 mmol/L)	—
Lipid disorder: cholesterol (fasting), high: < 18 years of age	170 to < 200 mg/dL (4.40 to < 5.15 mmol/L)	200 to < 300 mg/dL (5.15 to < 7.77 mmol/L)	≥ 300 mg/dL (≥ 7.77 mmol/L)	—
Lipid disorder: LDL (fasting), high: ≥ 18 years of age	130 to < 160 mg/dL (3.37 to < 4.12 mmol/L)	160 to < 190 mg/dL (4.12 to < 4.90 mmol/L)	≥ 190 mg/dL (≥ 4.90 mmol/L)	—

ULN = upper limit of normal.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
Lipid disorder: LDL (fasting), high: >2 to <18 years of age	110 to <130 mg/dL (2.85 to <3.34 mmol/L)	130 to <190 mg/dL (3.34 to <4.90 mmol/L)	≥190 mg/dL (≥4.90 mmol/L)	—
Lipid disorder: triglycerides (fasting), high	150 to 300 mg/dL (1.71 to 3.42 mmol/L)	>300 to 500 mg/dL (>3.42 to 5.7 mmol/L)	>500 to <1,000 mg/dL (>5.7 to 11.4 mmol/L)	>1,000 mg/dL (>11.4 mmol/L)
Magnesium, low	1.2 to <1.4 mEq/L (0.60 to <0.70 mmol/L)	0.9 to <1.2 mEq/L (0.45 to <0.60 mmol/L)	0.6 to <0.9 mEq/L (0.30 to <0.45 mmol/L)	<0.6 mEq/L (<0.30 mmol/L)
Phosphate, low: >14 years of age	2.0 mg/dL to <LLN (0.65 mmol/L to <LLN)	1.4 to <2.0 mg/dL (0.45 to <0.65 mmol/L)	1.0 to <1.4 mg/dL (0.32 to <0.45 mmol/L)	<1.0 mg/dL (<0.32 mmol/L)
Phosphate, low: 1 to 14 years of age	3.0 to <3.5 mg/dL (0.97 to <1.13 mmol/L)	2.5 to <3.0 mg/dL (0.81 to <0.97 mmol/L)	1.5 to <2.5 mg/dL (0.48 to <0.81 mmol/L)	<1.5 mg/dL (<0.48 mmol/L)
Phosphate, low: <1 year of age	3.5 to <4.5 mg/dL (1.13 to <1.45 mmol/L)	2.5 to <3.5 mg/dL (0.81 to <1.13 mmol/L)	1.5 to <2.5 mg/dL (0.48 to <0.81 mmol/L)	<1.5 mg/dL (<0.48 mmol/L)
Potassium, high	5.6 to <6.0 mEq/L or mmol/L	6.0 to <6.5 mEq/L or mmol/L	6.5 to <7.0 mEq/L or mmol/L	≥7.0 mEq/L or mmol/L
Potassium, low	3.0 to <3.4 mEq/L or mmol/L	2.5 to <3.0 mEq/L or mmol/L	2.0 to <2.5 mEq/L or mmol/L	<2.0 mEq/L or mmol/L
Sodium, high	146 to <150 mEq/L or mmol/L	150 to <154 mEq/L or mmol/L	154 to <160 mEq/L or mmol/L	≥160 mEq/L or mmol/L
Sodium, low	130 to <135 mEq/L or mmol/L	125 to <130 mEq/L or mmol/L	121 to <125 mEq/L or mmol/L	*<121* mEq/L or mmol/L
Uric acid, high	7.5 to <10.0 mg/dL (0.45 to <0.59 mmol/L)	10.0 to <12.0 mg/dL (0.59 to <0.71 mmol/L)	12.0 to <15.0 mg/dL (0.71 to <0.89 mmol/L)	≥15.0 mg/dL (≥0.89 mmol/L)

LLN = lower limit of normal.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Hematology				
Absolute $CD4^+$ count, low (not HIV infected): >5 years of age	300 to <400 cells/mm^3 (0.300×10^9 to $<0.400 \times 10^9$ cells/L)	200 to <300 cells/mm^3 (0.200×10^9 to $<0.300 \times 10^9$ cells/L)	100 to <200 cells/mm^3 (0.100×10^9 to $<0.200 \times 10^9$ cells/L)	<100 cells/mm^3 (0.100×10^9 cells/L)
Absolute lymphocyte count, low (not HIV infected): >5 years of age	600 to <650 cells/mm^3 (0.600×10^9 to $<0.650 \times 10^9$ cells/L)	500 to <600 cells/mm^3 (0.500×10^9 to $<0.600 \times 10^9$ cells/L)	350 to <500 cells/mm^3 (0.350×10^9 to $<0.500 \times 10^9$ cells/L)	<350 cells/mm^3 ($<0.350 \times 10^9$ cells/L)
Absolute neutrophil count, low: >7 days of age	800 to 1000 cells/mm^3 (0.800×10^9 to 1.000×10^9 cells/L)	600 to 799 cells/mm^3 (0.600×10^9 to 0.799×10^9 cells/L)	400 to 599 cells/mm^3 (0.400×10^9 to 0.599×10^9 cells/L)	<400 cells/mm^3 ($<0.400 \times 10^9$ cells/L)
Absolute neutrophil count, low: 2 to 7 days of age	1250 to 1500 cells/mm^3 (1.250×10^9 to 1.500×10^9 cells/L)	1000 to 1249 cells/mm^3 (1.000×10^9 to 1.249×10^9 cells/L)	750 to 999 cells/mm^3 (0.750×10^9 to 0.999×10^9 cells/L)	<750 cells/mm^3 ($<0.750 \times 10^9$ cells/L)
Absolute neutrophil count, low: ≤1 day of age	4000 to 5000 cells/mm^3 (4.000×10^9 to 5.000×10^9 cells/L)	3000 to 3999 cells/mm^3 (3.000×10^9 to 3.999×10^9 cells/L)	1500 to 2999 cells/mm^3 (1.500×10^9 to 2.999×10^9 cells/L)	<1500 cells/mm^3 ($<1.500 \times 10^9$ cells/L)
Fibrinogen, decreased	100 to <200 mg/dL (1.00 to <2.00 g/L) or 0.75 to $<1.00 \times$ LLN	75 to <100 mg/dL (0.75 to <1.00 g/L) or ≥0.50 to $<0.75 \times$ LLN	50 to <75 mg/dL (0.50 to <0.75 g/L) or 0.25 to $<0.50 \times$ LLN	<50 mg/dL (<0.50 g/L) or $<0.25 \times$ LLN or associated with gross bleeding

LLN = lower limit of normal.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Hematology (cont.)				
Hemoglobin, low: ≥13 years of age (male only) [k]	10.0 to 10.9 g/dL (6.19 to 6.76 mmol/L)	9.0 to <10.0 g/dL (5.57 to <6.19 mmol/L)	7.0 to <9.0 g/dL (4.34 to <5.57 mmol/L)	<7.0 g/dL (<4.34 mmol/L)
Hemoglobin, low: ≥13 years of age (female only) [k]	9.5 to 10.4 g/dL (5.88 to 6.48 mmol/L)	8.5 to <9.5 g/dL (5.25 to <5.88 mmol/L)	6.5 to <8.5 g/dL (4.03 to <5.25 mmol/L)	<6.5 g/dL (<4.03 mmol/L)
Hemoglobin, low: 57 days to <13 years of age (male and female) [k]	9.5 to 10.4 g/dL (5.88 to 6.48 mmol/L)	8.5 to <9.5 g/dL (5.25 to <5.88 mmol/L)	6.5 to <8.5 g/dL (4.03 to <5.25 mmol/L)	<6.5 g/dL (<4.03 mmol/L)
Hemoglobin, low: 36 to 56 days of age (male and female) [k]	8.5 to 9.6 g/dL (5.26 to 5.99 mmol/L)	7.0 to <8.5 g/dL (4.32 to <5.26 mmol/L)	6.0 to <7.0 g/dL (3.72 to <4.32 mmol/L)	<6.0 g/dL (<3.72 mmol/L)
Hemoglobin, low: 22 to 35 days of age (male and female) [k]	9.5 to 11.0 g/dL (5.88 to 6.86 mmol/L)	8.0 to <9.5 g/dL (4.94 to <5.88 mmol/L)	6.7 to <8.0 g/dL (4.15 to <4.94 mmol/L)	<6.7 g/dL (<4.15 mmol/L)
Hemoglobin, low: 8 to 21 days of age (male and female) [k]	11.0 to 13.0 g/dL (6.81 to 8.10 mmol/L)	9.0 to <11.0 g/dL (5.57 to <6.81 mmol/L)	8.0 to <9.0 g/dL (4.96 to <5.57 mmol/L)	<8.0 g/dL (<4.96 mmol/L)
Hemoglobin, low: ≤7 days of age (male and female) [k]	13.0 to 14.0 g/dL (8.05 to 8.72 mmol/L)	10.0 to <13.0 g/dL (6.19 to <8.05 mmol/L)	9.0 to <10.0 g/dL (5.59 to <6.19 mmol/L)	<9.0 g/dL (<5.59 mmol/L)

[k] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, hemoglobin grade should be based on values for the gender with which they identify (e.g., grade for a transgender female should be based on hemoglobin laboratory values for females).

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Hematology (cont.)				
INR, high (not on anticoagulation therapy)	1.1 to $<1.5\times$ ULN	1.5 to $<2.0\times$ ULN	2.0 to $<3.0\times$ ULN	$\geq 3.0\times$ ULN
Methemoglobin (% hemoglobin)	5.0% to $<10.0\%$	10.0% to $<15.0\%$	15.0% to $<20.0\%$	$\geq 20.0\%$
PTT, high (not on anticoagulation therapy)	1.1 to $<1.66\times$ ULN	1.66 to $<2.33\times$ ULN	2.33 to $<3.00\times$ ULN	$\geq 3.00\times$ ULN
Platelets, decreased	100,000 to $<125{,}000$ cells/mm^3 (100.000×10^9 to $<125.000\times10^9$ cells/L)	50,000 to $<100{,}000$ cells/mm^3 (50.000×10^9 to $<100.000\times10^9$ cells/L)	25,000 to $<50{,}000$ cells/mm^3 (25.000×10^9 to $<50.000\times10^9$ cells/L)	$<25{,}000$ cells/mm^3 ($<25.000\times10^9$ cells/L)
PT, high (not on anticoagulation therapy	1.1 to $<1.25\times$ ULN	1.25 to $<1.50\times$ ULN	1.50 to $<3.00\times$ ULN	$\geq 3.00\times$ ULN
WBC, decreased: >7 days of age	2000 to 2499 cells/mm^3 (2.000×10^9 to 2.499×10^9 cells/L)	1500 to 1999 cells/mm^3 (1.500×10^9 to 1.999×10^9 cells/L)	1000 to 1499 cells/mm^3 (1.000×10^9 to 1.499×10^9 cells/L)	<1000 cells/mm^3 ($<1.000\times10^9$ cells/L)
WBC, decreased: ≤ 7 days of age	5500 to 6999 (5.500×10^9 to 6.999×10^9 cells/L)	4000 to 5499 (4.000×10^9 to 5.499×10^9 cells/L)	2500 to 3999 (2.500×10^9 to 3.999×10^9 cells/L)	<2500 ($<2.500\times10^9$ cells/L)

ULN = upper limit of normal.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Urinalysis				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤250 mg	2+ or >250 to ≤500 mg	>2+ or >500 mg	—
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to <10 RBCs per high power field	≥10 RBCs per high power field	Gross, with or without clots or with RBC casts or intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	—

Table 7 Severity Grading for Elevated Total Bilirubin in Neonates

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neonates ≥35 Weeks Gestational Age				
<24 hours of age	4 to <7 mg/dL (68.4 to <119.7 μmol/L)	7 to <10 mg/dL (119.7 to <171 μmol/L)	10 to <17 mg/dL (171 to <290.7 μmol/L)	≥17 mg/dL (≥290.7 μmol/L)
24 to <48 hours of age	5 to <8 mg/dL (85.5 to <136.8 μmol/L)	8 to <12 mg/dL (136.8 to <205.2 μmol/L)	12 to <19 mg/dL (205.2 to <324.9 μmol/L)	≥19 mg/dL (≥324.9 μmol/L)
48 to <72 hours of age	8.5 to <13 mg/dL (145.35 to <222.3 μmol/L)	13 to <15 mg/dL (222.3 to <256.5 μmol/L)	15 to <22 mg/dL (256.5 to <376.2 μmol/L)	≥22 mg/dL (≥376.2 μmol/L)
72 hours to <7 days of age	11 to <16 mg/dL (188.1 to <273.6 μmol/L)	16 to <18 mg/dL (273.6 to <307.8 μmol/L)	18 to <24 mg/dL (307.8 to <410.4 μmol/L)	≥24 mg/dL (≥410.4 μmol/L)
7 to 28 days of age (breast feeding)	5 to <10 mg/dL (85.5 to <171 μmol/L)	10 to <20 mg/dL (171 to <342 μmol/L)	20 to <25 mg/dL (342 to <427.5 μmol/L)	≥25 mg/dL (≥427.5 μmol/L)
7 to 28 days of age (not breast feeding)	1.1 to <1.6× ULN	1.6 to <2.6× ULN	2.6 to <5.0× ULN	≥5.0× ULN

ULN = upper limit of normal.

Table 2 Severity Grading for Elevated Total Bilirubin in Neonates (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neonates < 35 Weeks Gestational Age				
32 to < 35 weeks gestational age and < 7 days of age	—	—	10 to < 14 mg/dL (171 to < 239.4 μmol/L)	≥ 14 mg/dL (≥ 239.4 μmol/L)
28 to < 32 weeks gestational age and < 7 days of age	—	—	6 to < 10 mg/dL (102.6 to < 171 μmol/L)	≥ 10 mg/dL (≥ 171 μmol/L)
< 28 weeks gestational age and < 7 days of age	—	—	5 to < 8 mg/dL (85.5 to < 136.8 μmol/L)	≥ 8 mg/dL (≥ 136.8 μmol/L)
7 to 28 days of age (breast feeding)	5 to < 10 mg/dL (85.5 to < 171 μmol/L)	10 to < 20 mg/dL (171 to < 342 μmol/L)	20 to < 25 mg/dL (342 to < 427.5 μmol/L)	≥ 25 mg/dL (≥ 427.5 μmol/L)
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 × ULN	1.6 to < 2.6 × ULN	2.6 to < 5.0 × ULN	≥ 5.0 × ULN

ULN = upper limit of normal.

Table 3 Severity Grading for Events Not Specifically Listed in Tables 1 and 2

Grade	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

REFERENCE

[HHS] U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, corrected version 2.1 [resource on the Internet]. 2017 [cited: 12 October 2021]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

Appendix *11*
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Product Name	IMP/NIMP Designation	Marketing Authorization Status in EEA/and/ /U.K.	Used within Marketing Authorization
GDC-6599	IMP (test product)	Not approved	Not applicable
GDC-6599 Placebo	IMP (Placebo)	Not approved	Not applicable
Mannitol (Aridol®/Osmohale®)	IMP (challenge agent)	Approved	Yes

EEA = European Economic Area; IMP = investigational medicinal product; U.K. = United Kingdom.

Appendix 12
Drugs Associated with QT Prolongation

Drugs associated with QT prolongation are prohibited within 1 month prior to screening (Study Visit 1) through the completion of the study at Visit 8. A list of drugs with known risk of QT prolongation is shown in Table 1. This list is subject to change (output date 15 November 2022); please consult crediblemeds.org for updated information and information on additional drugs with possible or conditional risk of QT prolongation.

Table 1 Drugs with a Known Risk of QT Prolongation

Generic Name	***Brand Names (Partial List)***
Aclarubicin (Only on Non-U.S. Market)	*Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin*
Amiodarone	*Cordarone, Pacerone, Nexterone*
Anagrelide	*Agrylin, Xagrid*
Arsenic trioxide	*Trisenox*
Astemizole (Removed from U.S. Market)	*Hismanal*
Azithromycin	*Zithromax, Zmax*
Bepridil	*Vascor*
Cesium Chloride	*Energy Catalyst*
Chloroquine	*Aralen*
Chlorpromazine	*Thorazine, Largactil, Megaphen*
Chlorprothixene (Only on Non-U.S. Market)	*Truxal*
Cilostazol	*Pletal*
Ciprofloxacin	*Cipro, Cipro-XR, Neofloxin*
Cisapride (Removed from US Market)	*Propulsid*
Citalopram	*Celexa, Cipramil*
Clarithromycin	*Biaxin, Prevpac*
Cocaine	*Cocaine*
Disopyramide	*Norpace*
Dofetilide	*Tikosyn*
Domperidone (Only on Non-US Market)	*Motilium, Motillium, Motinorm Costi, Nomit*
Donepezil	*Aricept*
Dronedarone	*Multaq*
Droperidol	*Inapsine, Droleptan, Dridol, Xomolix*

Table 1 Drugs with a Known Risk of QT Prolongation (cont.)

Erythromycin	*E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth*
Escitalopram	*Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil*
Flecainide	*Tambocor, Almarytm, Apocard, Ecrinal, Flécaine*
Fluconazole	*Diflucan, Trican*
Gatifloxacin (Removed from U.S. Market)	*Tequin*
Grepafloxacin (Removed from U.S. Market)	*Raxar*
Halofantrine (Only on Non-U.S. Market)	*Halfan*
Haloperidol	*Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol*
Hydroquinidine (Dihydroquinidine) (Only on Non-U.S. Market)	*Serecor*
Hydroxychloroquine	*Plaquenil, Quineprox*
Ibogaine (Only on Non-U.S. Market)	
Ibutilide	*Corvert*
Levofloxacin	*Levaquin, Tavanic*
Levomepromazine (Methotrimeprazine) (Only on Non-U.S. Market)	*Nosinan, Nozinan, Levoprome*
Levomethadyl acetate (Removed from U.S. Market)	*Orlaam*
Levosulpiride (Only on Non-US Market)	*Lesuride, Levazeo, Enliva*
Meglumine antimoniate	*Glucantime*
Mesoridazine (Removed from US Market)	*Serentil*
Methadone	*Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon*
Mobocertinib	*Exkivity*
Moxifloxacin	*Avelox, Avalox, Avelon*
Nifekalant (Only on Non-US Market)	*Shinbit*
Ondansetron	*Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax*

Table 1 Drugs with a Known Risk of QT Prolongation (cont.)

Oxaliplatin	*Eloxatin*
Papaverine HCl (Intracoronary)	
Pentamidine	*Pentam*
Pimozide	*Orap*
Probucol (Removed from US Market)	*Lorelco*
Procainamide	*Pronestyl, Procan*
Propofol	*Diprivan, Propoven*
Quinidine	*Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora*
Roxithromycin (Only on Non-US Market)	*Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin*
Sertindole	*Serdolect, Serlect*
Sevoflurane	*Ultane, Sojourn*
Sotalol	*Betapace, Sotalex, Sotacor*
Sparfloxacin (Removed from US Market)	*Zagam*
Sulpiride (Only on Non-US Market)	*Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor*
Sultopride (Only on Non-US Market)	*Barnetil, Barnotil, Topral*
Terfenadine (Removed from US Market)	*Seldane*
Terlipressin (Only on Non-US Market)	*Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss*
Terodiline (Only on Non-US Market)	*Micturin, Mictrol*
Thioridazine	*Mellaril, Novoridazine, Thioril*
Vandetanib	*Caprelsa*

TdP = torsades de pointes.

Note: All drugs listed above are:

Known risk of TdP: *Substantial evidence supports the conclusion that these drugs prolong the QT interval AND are clearly associated with a risk of TdP, even when taken as directed in official labeling.*

Drugs to avoid in congenital long QT*: Substantial evidence supports the conclusion that these drugs pose a risk of TdP for patients with congenital long QT. Drugs on this list include those in the above risk category and other drugs that do not prolong the Qt interval per se, but they have a theoretical risk of causing arrhythmia that is based on their known stimulant actions on the heart.*

REFERENCE

Woosley RL, Heise CW , Gallo T, et al., QTdrugs List, [resource on the Internet]. 2023 [updated: 15 November 2022; cited: 2 February 2023]. Available from: https://crediblemeds.org/.

Signature Page for Protocol - GA43590 - TRPA1 INHIBITOR (2) - v4 - Published
System identifier: RIM-CLIN-532976

Approval Task	[redacted] Company Signatory 03-May-2024 15:42:47 GMT+0000