Document Type:	Study protocol
Official Title:	Randomized, double-blind, parallel group, phase 2b dose-finding, efficacy and safety study of 12-week twice daily oral administration of BAY 1817080 compared to placebo in the treatment of refractory and/or unexplained chronic cough (RUCC)
NCT Number:	NCT04562155
Document Date:	28-Apr-2021

Title Page

Protocol Title:

Randomized, double-blind, parallel group, Phase 2b dose-finding, efficacy and safety study of 12-week twice daily oral administration of BAY 1817080 compared to placebo in the treatment of refractory and/or unexplained chronic cough (RUCC)

Protocol Number:	20393
Protocol Version:	3.0
Amendment Number:	2
Compound Number:	BAY 1817080
Study Phase:	Phase 2b
Short Title:	Dose-finding, efficacy and safety study of BAY 1817080 in the treatment of refractory and/or unexplained chronic cough
Acronym:	PAGANINI

Sponsor Name and Legal Registered Address:

Non-US:	Bayer AG D-51368 Leverkusen, Germany
US Territory:	Bayer Healthcare Pharmaceuticals Inc. 100 Bayer Boulevard, P.O. Box 915 Whippany NJ 07981-0915, USA

Regulatory Agency Identifier Numbers:

IND:	139697
EudraCT:	2019-004169-42

Protocol Amendment Date: 28 APR 2021

Name: PPD Role: PPD

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

Medical Monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	28 APR 2021
Amendment 1	17 JUL 2020
Amendment CZE-1	30 APR 2020
Original Protocol	19 DEC 2019

Amendment 2 (28 APR 2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The main purpose of this amendment is to remove the description of the interim analysis. Due to unexpectedly rapid recruitment, the amount of 12-week efficacy and safety data at the planned interim analysis would not have been sufficient for a preliminary dose decision. Therefore, no interim analysis will be performed.

Section # and Name	Description of Change	Brief Rationale
9.5 Interim Analyses	Description of interim analyses was deleted and the statement “not applicable to this study“ was included.	Due to unexpectedly rapid progression of the study, no interim analysis will be performed. Primary analysis will be conducted once all participants have completed 12 weeks of intervention, as described in Section 9.4.2.
9.4.1 General considerations	The term “database lock“ was changed to “unblinding of the database”.	To reflect the current convention in terminology of the company
4.3 Justification for Dose	The values of awake cough counts obtained from the proof of concept study for RUCC (study 18184) were corrected (26.1% instead of 21.1% for the maximum technically feasible dose of 750 mg BID or the next lower dose of 200 mg BID of BAY 1817080 and 24.4% instead of 22.5% for the placebo).	Correction of error
Title page	Sponsor signatory was removed and a statement added that this is an electronically generated document that does not bear any sponsor signatures.	To reflect the current convention of the company
Title page	The name of the sponsor’s medically responsible person was updated.	The previous medically responsible person is no longer involved in this study

Section # and Name	Description of Change	Brief Rationale
Title page Header throughout the document	Protocol version number was included in the Title page and removed from the header. Date was added in the header.	To reflect the current convention of the company

Table of Contents

Table of Tables

Table of Figures

1. Protocol Summary

1.1 Synopsis

Protocol Title: Randomized, double-blind, parallel group, Phase 2b dose-finding, efficacy and safety study of 12-week twice daily oral administration of BAY 1817080 compared to placebo in the treatment of refractory and/or unexplained chronic cough (RUCC)

Short Title: Dose-finding, efficacy and safety study of BAY 1817080 in the treatment of RUCC

Rationale: The objective of this study is to identify the optimal dose of P2X3 receptor antagonist BAY 1817080 in patients with RUCC and further assess efficacy and characterize safety and tolerability profile of BAY 1817080.

Objectives and Endpoints:

Objectives	Endpoints
Primary	**Primary Efficacy Endpoints**
• Assess the efficacy of P2X3 receptor antagonist BAY 1817080 as compared with placebo in terms of change in 24-hour cough count from baseline to week 12	• Change from baseline in 24-hour cough count (measured by cough recording digital wearable monitoring device) after 12 weeks of intervention
Secondary	**Secondary Endpoints**
• Further assess efficacy of BAY 1817080	**Secondary Efficacy Endpoints** • Percentage of participants with a ≥30% reduction from baseline in 24-hour cough count after 12 weeks of intervention (measured by cough recording digital wearable monitoring device) • Change from baseline in 24-hour cough count after 2, 4, and 8 weeks of intervention (measured by cough recording digital wearable monitoring device) • Change from baseline in awake cough frequency per hour after 2, 4, 8 and 12 weeks of intervention (measured by cough recording digital wearable monitoring device) • Change from baseline in cough related quality of life (measured by Leicester Cough Questionnaire [LCQ]) after 12 weeks of intervention • Change from baseline in cough severity after 12 weeks of intervention (measured by Cough Severity Visual Analogue Scale [VAS]) • Percentage of participants with a ≥30 scale units reduction from baseline after 12 weeks of intervention (measured by cough Severity VAS) • Percentage of participants with a ≥1.3-point increase from baseline after 12 weeks of intervention (measured with LCQ Total Score)
• Further characterize safety and tolerability profile of BAY 1817080	**Safety and Tolerability Evaluation** • Frequency and associated severity of treatment-emergent adverse events (TEAEs)

Overall Design:

Disclosure Statement: This is a double-blind, parallel group intervention study.

Intervention Model: Parallel group

Primary Purpose: Treatment

Number of Arms: 4 arms including

- Active intervention: 150 mg BID
- Active intervention: 75 mg BID
- Active intervention: 25 mg BID
- Placebo

Blinding: Participant, investigator and sponsor

Number of Participants: Approximately 337 participants will be screened to achieve 236 randomly assigned to study intervention and 200 evaluable participants for an estimated total of 50 evaluable participants per intervention group.

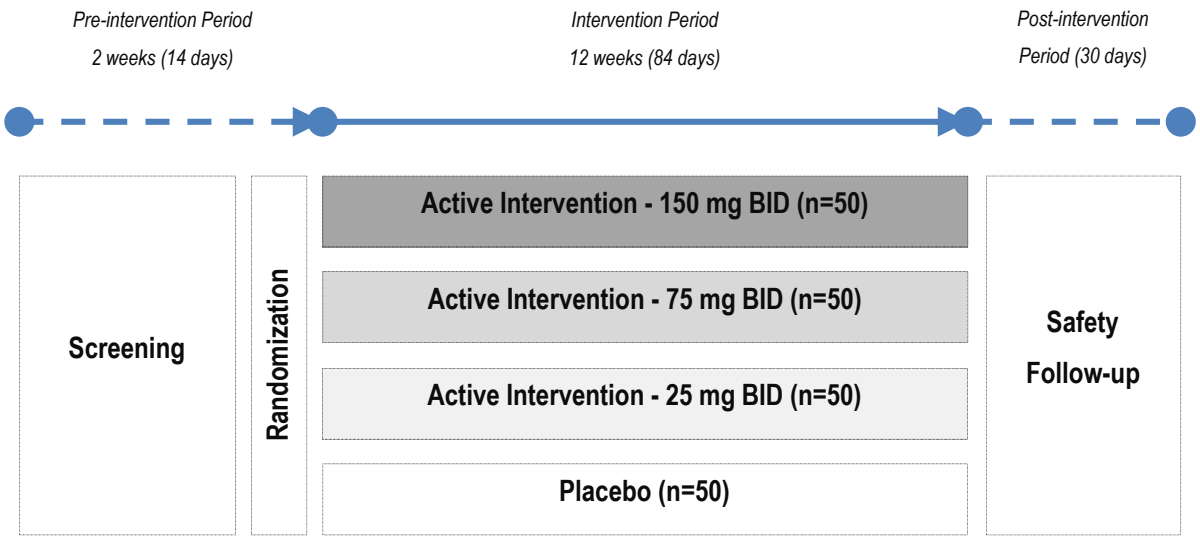
Intervention Groups and Duration:

Study periods	**Duration**
Screening Intervention Safety Follow-up	14 days (2 weeks) 84 days (12 weeks) 30 days (approximately 4 weeks)
Total study duration	**128 days (approximately 18 weeks)**

Data Monitoring Committee: No.

1.2 Schema

Figure 1–1: Study design



Abbreviations: BID = bis in die (twice daily); n= number of completers

1.3 Schedule of Activities (SoA)

Procedure	Screening	Intervention							Safety Follow-up
Visit	**V1**	**V2[1]**		**V3**	**V4**	**V5**	**V6[2]/TV[3]**		**SFU[4]**
Day (Relative to start of intervention)	**-16 up to -14 days**	**-1**	**0**	**14±2**	**28±2**	**56±2**	**83±2**	**84±2**	**30±5**
Week (Relative to start of intervention)	**-2**			**2**	**4**	**8**	**12**		
Informed consent	X								
Baseline characteristics and medical history									
Demography	X								
Medical history and concurrent medical conditions	X		X						
Eligibility assessment and randomization									
Inclusion and exclusion criteria	X		X						
Screening registration in IWRS	X								
Randomization registration in IWRS	X[5]								
Confirmation of randomization in IWRS[6]			X						
Study intervention, pharmacokinetics and biomarkers									
Visit/EoI registration in IWRS				X	X	X		X	
Dispensation of study intervention			X[7]	X	X	X			
Study intervention return and accountability				X	X	X		X	
Blood sample for PK[8]			X		X	X		X[9]	
Blood sample for biomarkers			X[10]		X			X[11]	
Blood sample for genetics[12]			X						
Safety-related assessments									
Physical examination, including weight and height[13]	X		X					X	
Vital signs	X[14]		X	X	X	X		X	X
12-lead ECG	X							X	X
Blood sample for central safety laboratory testing[15]	X				X	X		X	X
Collection of samples for COVID-19 testing[16]	X		X		X	X		X	X
Pregnancy testing, if applicable[17]	X		X		X	X		X	X
Spirometry[18]	X								

Procedure	Screening	Intervention							Safety Follow-up
Visit	**V1**	**V2[1]**		**V3**	**V4**	**V5**	**V6[2]/TV[3]**		**SFU[4]**
Day (Relative to start of intervention)	**-16 up to -14 days**	**-1**	**0**	**14±2**	**28±2**	**56±2**	**83±2**	**84±2**	**30±5**
Week (Relative to start of intervention)	**-2**			**2**	**4**	**8**	**12**		
Adverse events[19]	X		X	X	X	X		X	X
Prior and concomitant medication	X		X	X	X	X		X	X
Survival status[20]									X
Efficacy / patient report outcomes assessments									
Dispensation of cough recording device	X	X		X	X	X	X		
24-hour cough recording[21]	X	X		X	X	X	X		
Dispensation of handheld device for diary completion	X								
SCCD data collection[22]	←==========→								
Cough Severity VAS[23]	←==========→								
LCQ[24]	X		X	X	X	X		X	X
EQ-5D-5L[24]	X		X	X	X	X		X	X
PGI-S[24]	X		X	X	X	X		X	X
PGI-C[24]				X	X	X		X	X

Abbreviations: ECG = electrocardiogram; EoI = end of intervention; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level Scale; IWRS = Interactive Web Response System; LCQ = Leicester Cough Questionnaire; PK = pharmacokinetics; PGI-C = patient global impression of change; PGI-S = patient global impression of severity; SCCD = Severity of Chronic Cough Diary; SFU = safety follow-up; TV = termination visit; V = visit

1. Visit 2 will be a 2-day visit. On the first day the cough recording device will be dispensed and cough recording started by the participant. On the second day, only after cough recording has been completed other procedures for Visit 2 can be performed.
2. Visit 6 will be a consecutive 2-day visit. On the first day the cough recording device will be dispensed and cough recording started by the participant. On the second day, only after cough recording has been completed other procedures for Visit 6 can be performed.
3. In case of premature discontinuation of the study intervention before week 12, a termination visit (TV) should be conducted. All procedures planned for Visit 6, with the exception of the sparse PK sampling and biomarker sampling, should be performed at the TV, preferably on the day of the last tablet intake.
4. The safety follow-up visit will be performed 30 (±5) days after intake of the last tablet.
5. To assure timely drug supply to each study site, the recording of randomization must be completed at least 1 day but not later than 4 days after Visit 1 (before Visit 2).
6. The recording of randomization in IWRS of a participant who is eligible for intervention must be repeated on the day of the planned start of intervention. This will be considered as confirmation of randomization and will trigger the notification to the site about the study medication assignment.
7. The first dose of study intervention will be administered only after the 24h cough recording has been completed and the eligibility of the participant has been confirmed.
8. PK sampling timing: at Visit 2 and Visit 6: pre-dose, 2 hours and 4 hours post-dose; at Visit 4 and Visit 5: 6 hours post-dose (±15 min time window allowed for all samples). More details on PK sampling and collection of information about the type of meal taken in timely relation to PK sampling and drug intake are provided in Section 8.5.
9. At TV, sparse PK sampling will not be conducted.
10. The sample has to be taken prior to the start of study intervention.
11. At TV, biomarker sampling will not be conducted.
12. Blood sampling for genetics will have to be taken on Day 0 of Visit 2.
13. Height will be measured at Visit 1 only.
14. Blood pressure measurements can be repeated once during the screening visit if medically justified (e.g. in order to avoid suspected “white-coat hypertension”).
15. Hematology, chemistry and coagulation tests are to be conducted at a central laboratory every 4 weeks.
16. An oropharyngeal swab sample must be collected for quantitative measurement of the virus and a serum sample for the measurement of antibodies.
17. Pregnancy testing will be only applicable for women of childbearing potential. A serum test will be performed at screening and urine testing will be performed at all other site visits.
18. Spirometry results must not be older than 3 months prior to screening.
19. Adverse events will be collected from signing the informed consent until the follow-up visit at the time points specified in the SoA.
20. If a participant does not show up at the site for the planned safety follow-up visit, the survival status has to be checked.
21. Recording of cough with the cough recording device worn by participant for 24 hours.
22. Recording of data about cough severity on SCCD by participant every day on a handheld device.
23. Cough Severity VAS will be completed by the participant every day on a handheld device.
24. LCQ, EQ-5D-5L, PGI-S, and PGI-C will be completed by the participant on a tablet device during the study visits.

2. Introduction

Cough is one of the symptoms for which patients most frequently seek medical attention. In most patients, cough manifests itself as an acute cough, e.g., due to an upper respiratory infection, lasts a few days to weeks, and is usually self-limiting, thus resolves without any medical treatment. In general, cough is classified, on the basis of its duration, into acute (< 3 weeks), sub-acute (3-8 weeks) and chronic (> 8 weeks). The prevalence of chronic cough, i.e., a cough that is not self-limiting, is estimated to be around 10% in the adult population.

Chronic cough is a feature of many common respiratory diseases (e.g., chronic obstructive pulmonary disease, asthma) and some non-respiratory conditions (e.g., gastroesophageal reflux and rhinosinusitis) (1, 2), and it may be the presenting symptom of patients with some rarer conditions (e.g., idiopathic pulmonary fibrosis and eosinophilic bronchitis). In up to 50% of the chronic cough cases, the cough is refractory despite extensive investigation and treatment trials. In other patients with chronic cough, no potential underlying etiology is found – those are patients with a so-called idiopathic (or unexplained) chronic cough.

Despite the distinction above, publications often summarize both refractory and idiopathic chronic cough simply as refractory chronic cough. In this study protocol, both will be jointly referred to as refractory and/or unexplained chronic cough (RUCC).

In the majority of patients with RUCC, it has been postulated that sensitized nerve fibers play a prominent role after they fail to return to a normal quiescent state. This situation has been described in the literature as “cough hypersensitivity syndrome.” Patients with RUCC typically present with a mean age of about 65 years, and about two thirds of these patients are female (3, 4).

In a normal physiological state, noxious stimuli lead to a protective cough, while innocuous stimuli are not recognized by the cough receptors. In patients with cough hypersensitivity syndrome, however, even small, innocuous stimuli lead to the urge to cough. In fact, it was shown, in the experimental set-up of cough challenges, that the concentration of the tussive agent capsaicin, required to elicit 5 coughs within 15 seconds, is about 100 times lower in patients with RUCC than in healthy individuals (5). The underlying nerve damage usually occurs after an initial injury (often a viral infection) and is thought to be associated with a local neuropathy leading to throat-clearing among other responses.

While cough is a key protective reflex preventing aspiration and promoting airway clearance, cough in patients with RUCC is mainly pathologic, does not serve as an airway-protective mechanism and has a major impact on physical and psychological aspects of quality of life. Among the physical complications reported by a large proportion of patients with RUCC are exhaustion/fatigue, insomnia, breathlessness, vomiting and urinary incontinence (the latter predominately reported by women). Psychological complications with a high prevalence in patients with RUCC are depression, anxiety and embarrassment as well as interference with social life. Most patients with RUCC are able to identify the triggers of their cough, such as talking, singing, laughing, strong odors, strong foods or change in air temperature or quality.

A well-established expert panel have proposed a chronic cough algorithm for the management of patients > 15 years of age with cough lasting > 8 weeks, as clearly outlined by Irwin et al. 2006 (Figure 3) (6).

The evaluation of chronic cough is largely based on anatomic diagnostic protocols focused on the most common causes. The evidence supporting such protocols is limited and etiologic

work-up can occasionally be extensive, costly, and low yield. Sequential empiric therapy for the most common causes of chronic cough has thus been recommended instead. Identifying the specific patient concern allows individualization of the extent of the diagnostic evaluation and treatment as described by Achilleos et al. 2016 (Table 1) (7).

2.1 Study Rationale

The objective of this study is to identify the optimal dose of the P2X3 receptor antagonist BAY 1817080 in patients with RUCC and to further assess efficacy and characterize the safety and tolerability profile of BAY 1817080 following a 12-week twice daily oral treatment

2.2 Background

There are currently no specifically approved drugs for the treatment of RUCC. Current guideline-approved treatment options for the management of patients with RUCC include only empiric treatments than cause-directed therapies. The ERS 2019 guidelines on the diagnosis and treatment of chronic cough in adults and children incorporate all recent advances in chronic cough pathophysiology, diagnosis and treatment (8).

P2X3 ion channel receptors are expressed by airway vagal afferent nerves and contribute to the ATP-driven hypersensitization of sensory neurons, thus contributing to the induction of pathologic cough. Recently developed P2X3 receptor antagonists that block these receptors have been investigated in improved animal models of cough using validated cough frequency measurement tools and demonstrated a therapeutic promise. Extrapolating from the guinea pig cough model, and with a better understanding of neuronal activation and sensitization together with their signal processing in the brain, P2X3 antagonism mode of action has been further validated in Phase 2 clinical trials for the treatment of RUCC (9).

Bayer has proposed a clinical development plan intended to provide an efficacious and safe treatment option indicated for patients diagnosed with RUCC. The implementation of this clinical development plan, within an efficient time and resources frame, aims to generate strong scientific and clinical evidence and recommendations supporting the use of this medication.

The present Phase 2b clinical study intends to evaluate three different twice daily oral doses of a selective P2X3 receptor antagonist (BAY 1817080) and compare them to placebo during a period of 12 weeks aiming to identify the most efficacious, tolerable and safe dose to advance the drug into a Phase 3 of development.

2.3 Benefit/Risk Assessment

2.3.1 Summary

Chronic cough is a common and disabling disorder affecting approximately 5-10% of the adult population (10). Currently, there is no approved treatment for refractory chronic cough. Medicines, such as gabapentin and morphine, are used off-label in patients with refractory chronic cough, however they have limited efficacy and lead to a high rate of side effects. The burden of the disease and the limitations of currently available off-label use treatment modalities cause a serious unmet medical need.

The P2X3 antagonist gefapixant and other compounds are currently in clinical development for refractory chronic cough. Blocking of P2X3 counteracts purine ATP-evoked hyper-sensitization of afferent nerves, leading to a cessation/reduction of pathological coughing. Of note, an effect of P2X3 antagonism (gefapixant) on capsaicin- or citric-acid-evoked cough for

either healthy volunteers or refractory chronic cough patients was not observed, thus suggesting that the protective cough reflex remains unaffected by this mode-of-action, and only the pathological cough hypersensitivity syndrome is the therapeutic target for this mechanism (11).

BAY 1817080 is a potent and selective P2X3 antagonist, which preferentially blocks the homomeric P2X3 channel. BAY 1817080 showed a strong effect on airway sensory afferent activation by inhibition of depolarization of the human and guinea pig vagus nerve prepared from lung tissues. Beneficial effects of BAY 1817080 on cough frequency and severity were demonstrated in a Proof-of-Mechanism/Proof-of-Concept Phase 2a clinical trial with refractory chronic cough patients (9).

Benefit/risk ratio for BAY 1817080 is considered favorable for the planned study.

2.3.2 Potential Benefits

Administration of BAY 1817080 may be associated with the following benefits for patients with refractory chronic cough:

- Reduction in cough frequency, severity and urgency, which is expected to be associated with increased quality-of-life (QoL) and social functioning
- Relief from physical and psychological complications of cough, such as exhaustion/fatigue, insomnia, breathlessness, urinary incontinence, difficulties in speaking, depression and anxiety.

Recently generated evidence from a Proof-of-Mechanism/Proof-of-Concept Phase 2a clinical trial corroborates the potential benefit of this mode-of-action and is supportive of further developing BAY 1817080 as a therapeutic option for patients with refractory chronic cough (9). During the aforementioned Phase 2a study, BAY 1817080 was tested in four different doses of formulation A in patients with RUCC. Twice daily administration of 50 mg, 200 mg and 750 mg (formulation A) resulted in a 24-hour cough count reduction with -18.4%, -22% and -25%, respectively (placebo-corrected values). Of note, formulation B will be administered in the current Phase 2b dose-finding study as outlined in this protocol.

2.3.3 Risks and Undesirable Effects

2.3.3.1 Taste-Related AEs

Taste-related AEs have been observed dose-dependently in up to about 20% of study participants at a dose of 750 mg twice daily (BID; formulation A). This highest dose of 750 mg BID (formulation A) is expected to correspond to approximately 150 mg BID of formulation B as described thoroughly in the latest available version of the Investigator's Brochure (IB) and throughout this protocol. Taste-related AEs have also been reported for the P2X3 antagonist gefapixant (12).

To date, the influence of BAY 1817080 on taste perception has been investigated in a limited number of study participants only. In these studies, the change in taste perception was reported as being non-serious and mild. Changes were fully reversible after the end of treatment with BAY 1817080. No participants discontinued the treatment because of taste disturbances.

Study 18184 (9) was a two-part study, investigating safety and pharmacokinetics (PK) of BAY 1817080 in healthy volunteers (Part 1) and safety, efficacy and PK in patients with refractory chronic cough (Part 2). In Part 1, the frequency of the taste-related AEs was evenly

distributed between participants receiving active treatment with BAY 1817080 (3 participants; 8.6%) and participants receiving placebo (1 participant; 8.3%). In Part 2 of study 18184, overall 10 out of 40 participants treated reported a taste-related AE. Some of the AEs lasted for two or more consecutive treatment intervals with different doses. If evaluated by dose, 5.1% of participants had a taste-related AE starting or ongoing at the 10 mg dose, 10.3% at the 50 mg dose, 15.4 % at the 200 mg dose, and 20.5% at the 750 mg dose. When extrapolated to doses of formulation B, 50 mg, 200 mg and 750 mg BID of formulation A are expected to correspond to approximately 25 mg, 75 mg and 150 mg BID of formulation B, which are to be assessed in the current Phase 2b study.

Under placebo, 2.5% of participants reported a taste-related AE. The changes in taste perception were reported as being mild in all participants, and all participants had recovered from the taste-related AEs at the end of the study.

At the highest dose of 150 mg BID (formulation B; corresponding to a target dose of approximately 750 mg BID of formulation A), taste-related AEs are expected at rates of equal or less than 20%.

In this study, the frequency of taste-related AEs will be evaluated, including the assessment of how bothersome the AEs were perceived to be.

At this stage of clinical development, taste disturbance is regarded an identified risk.

2.3.3.2 Antithrombin III Activity Increase

In study 18184 (9) (Part 1), antithrombin III (ATIII) activity increases were observed in healthy participants treated with 200 mg and 750 mg BID of BAY 1817080 (formulation A). Effect was first observed 3 days after the first dose. Increase was up to ~20% above baseline in the 200 mg BID group, and up to ~30% above baseline in the 750 mg BID group (200 mg and 750 mg BID of formulation A are expected to correspond to approximately 75 and 150 mg BID of formulation B).

In study 18184 (Part 2), in patients with refractory chronic cough, there were similar time and dose-dependent increases of ATIII activity observed as in the healthy volunteers in Part 1 of the study.

No changes in coagulation parameters were observed and no signs of bleeding/bruising related to BAY 1817080 were observed in study 18184 or other studies, to date, with BAY 1817080.

Furthermore, there is no established clinical relevance linked to increased ATIII activity in medical literature. Therefore, it is concluded that at this stage of development, the increase in ATIII activity can be considered as not clinically relevant.

ATIII activity will be measured in this study. Coagulation parameters (prothrombin time (Quick), activated partial thromboplastin time (aPTT), fibrinogen, international normalized ratio (INR)) will be monitored regularly during the study as part of safety laboratory assessments.

Increased ATIII activity at this stage of development is regarded a potential risk.

2.3.3.3 Potential Decrease in Heart Rate and Diastolic Blood Pressure

In study 18184, a decrease in diastolic blood pressure (DBP) (4-7 mmHg) and heart rate (HR) (5-11 bpm) was observed in the highest dose group (750 mg BID formulation A corresponding to approximately 150 mg BID of formulation B) in healthy participants (Part 1;

mainly in 2-3 participants with high baseline values). The decrease in DBP and HR was not observed in patients with refractory chronic cough (Part 2).

In the absence of AEs related to the changes in DBP and HR, such as dizziness or syncope, this observation was considered as not clinically significant.

Decrease in HR and DBP at this stage of development is regarded as potential risk. HR and blood pressure will be monitored in this study.

2.3.3.4 Potential Changes in Liver Function Laboratory Parameters

In one of two in vitro assays, BAY 1817080 was found to be an inhibitor of bile salt export pump (BSEP). No other risk factors have been identified pre-clinically at relevant exposures, including absence of signals for mitochondrial toxicity. In GLP animal toxicology studies, no changes in liver function laboratory parameters have been observed.

To date, clinically no changes in total bile acids or liver function laboratory parameters related to BAY 1817080 have been observed.

Changes in liver function values at this stage of development are regarded as a potential risk. Liver-specific exclusion criteria and discontinuation rules have been defined. Liver function laboratory parameters will be assessed at 4-weekly intervals, i.e., at every visit. Investigators and participants should be alerted regarding non-specific symptoms which may be associated with liver dysfunction, including anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting, malaise, jaundice, fever, and rash. Information on these symptoms should be asked for in case of abnormal liver laboratory values (see Section 8.3.6) or any other suspicion of liver dysfunction. The study participants should be reminded to contact the study site immediately, if they are concerned about such symptoms and unscheduled liver laboratory assessments should be considered.

2.3.3.5 Reproductive Toxicity

Studies on reproductive and developmental toxicity of BAY 1817080 were conducted in rats and rabbits. No effects of BAY 1817080 on male/female reproduction, fertility or developmental toxicity have been detected with multiples of exposures relative to the anticipated human therapeutic exposures of about 6-fold (rats) and 0.8-fold (rabbits).

Women of childbearing potential must use an acceptable effective contraceptive method when receiving BAY 1817080. The use of highly effective methods of contraception will be allowed for women of child bearing potential (WOCBP) during the conduct of this Phase 2 study.

2.3.3.6 Potential Phototoxicity

BAY 1817080 was weakly phototoxic (Photoirritation factor, PIF = 17.7) in an in vitro phototoxicity assay at concentrations clearly exceeding the expected human maximum plasma concentration. In addition, reversible affinity to pigmented tissues (eye, skin) was seen in rats. In study 18184 (9), no AEs potentially linked to phototoxicity were observed.

Based on literature data (13), a PIF <25 derived from the in vitro assay is very unlikely to translate into in vivo phototoxicity. Nonetheless, as a precautionary measure, excessive exposure to sunlight should be avoided during the intervention period. Participants will be advised to use conventional ultraviolet (UV) sunscreens, to avoid prolonged sunbathing especially when traveling to a different geographical area with greater sunshine, and also to

avoid the use of solarium. They are also advised to use sunglasses if exposed to direct or excessive sunlight.

2.3.3.7 Risk of contracting SARS-CoV-2 infection during study participation

As long as the COVID-19 pandemic situation is ongoing, there is a risk of contracting a SARS-CoV-2 infection during the time period of study participation. Only SARS-CoV-2 virus RNA and IgG tests negative participants without any symptoms suggestive of COVID-19 infection will be included into this study. Given the global setting of the PAGANINI clinical trial, testing, as well as obtaining further information regarding symptoms suggestive of COVID-19 infection[1], will be part of the screening visit and subsequent visits (as applicable in accordance with guidance from the relevant regional and local public health authorities). Both quantitative detection and viral load analysis of SARS-CoV-2 through quantitative reverse transcription polymerase chain reaction (qRT-PCR) will be performed throughout the study. If a participant becomes SARS-CoV-2 virus RNA test positive during study participation, the investigator will have to decide whether remaining in the study is compatible with participant's and site personnel's safety and well-being.

[1] Common COVID-19 related symptoms could include (but are not limited to): fever over 38°C in the past 4 weeks; persistent chronic cough that exacerbated further in the past 4 weeks; chills; body aches; loss of smell and/or taste; headache; sore throat; fatigue.

3. Objectives and Endpoints

The objective of this study is to identify the optimal dose of P2X3 receptor antagonist BAY 1817080 in patients with RUCC and further assess efficacy and characterize safety and tolerability profile of BAY 1817080

Objectives	Endpoints
Primary	**Primary Efficacy Endpoint**
• Assess the efficacy of P2X3 receptor antagonist BAY 1817080 as compared with placebo in terms of change in 24-hour cough count from baseline to week 12	• Change from baseline in 24-hour cough count (measured by cough recording digital wearable monitoring device) after 12 weeks of intervention
Secondary	**Secondary Endpoints**
• Further assess efficacy of BAY 1817080	**Secondary Efficacy Endpoints** • Percentage of participants with a ≥30% reduction from baseline in 24-hour cough count after 12 weeks of intervention (measured by cough recording digital wearable monitoring device) • Change from baseline in 24-hour cough count after 2, 4, and 8 weeks of intervention (measured by cough recording digital wearable monitoring device) • Change from baseline in awake cough frequency per hour after 2, 4, 8 and 12 weeks of intervention (measured by cough recording digital wearable monitoring device) • Change from baseline in cough related quality of life (measured by Leicester Cough Questionnaire [LCQ]) after 12 weeks of intervention • Change from baseline in cough severity after 12 weeks of intervention (measured by Cough Severity Visual Analogue Scale [VAS]) • Percentage of participants with a ≥30 scale units reduction from baseline after 12 weeks of intervention (measured by cough Severity VAS) • Percentage of participants with a ≥1.3-point increase from baseline after 12 weeks of intervention (measured with LCQ Total Score)
• Further characterize safety and tolerability profile of BAY 1817080	**Safety and Tolerability Evaluation** • Frequency and associated severity of treatment-emergent adverse events (TEAEs)

Objectives	Endpoints
Other Pre-specified	**Exploratory Endpoints**
• Further describe the efficacy profile of BAY 1817080 through the impact of intervention as patient reported outcomes • Assess psychometric and other measurement properties of the newly developed SCCD	• Change from baseline in daily cough severity after 12 weeks of intervention (measured by the Severity of Chronic Cough Diary [SCCD]) • Change from baseline in night cough frequency per hour after 2, 4, 8, and 12 weeks of intervention (measured by cough recording digital wearable monitoring device) • Percentage of participants with a $\geqslant$50% and $\geqslant$70% reduction from baseline in 24-hour cough count after 12 weeks of intervention • Change from baseline in daily cough severity after 2, 4, and 8 weeks of intervention (measured by SCCD) • Change from baseline in cough severity after 2, 4, and 8 weeks of intervention (measured by Cough Severity VAS) • Change from baseline in cough related quality of life after 2, 4, and 8 weeks of intervention (measured by LCQ) • Patient Global Impression of Change (PGI-C) and change from baseline in Patient Global Impression of Severity (PGI-S), after 2, 4, 8 and 12 weeks of intervention. • Change from baseline in Health-related quality of Life (HrQoL) after 2, 4, 8 and 12 weeks of intervention (as measured by EQ-5D-5L)
• To investigate the pharmacokinetics of BAY 1817080 over the dose range of 25-150 mg BID in patients with RUCC	• Systemic exposure of BAY 1817080 in patients with RUCC
• To further investigate the study intervention and similar drugs (i.e., mode-of-action-related effects and / or safety) and to further investigate pathomechanisms deemed relevant to pulmonary diseases and associated health problems	• Blood biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers) at baseline, week 4, and week 12

Objectives	Endpoints
• To evaluate potential associations between disease-associated genotypic information and clinical efficacy and / or pharmacodynamics effects	• Evaluation of clinical efficacy parameters by repertoire or frequency of genetic alterations in the relevant pathways
• To further evaluate the impact of the disease and associated comorbidities	• Sleep disturbance (prevalence and impact) associated with cough in patients with RUCC • Frequency of urinary incontinence associated with cough in patients with RUCC • Other pre-specified endpoints, if any, are specified in the statistical analysis plan (SAP)

Estimand for the primary efficacy objective

The estimand of interest to assess the primary efficacy objective of the study is the effect of the intervention in those participants who tolerate the intervention, adhere to the intervention schedule and follow all relevant protocol procedures.

The attributes of the estimand are as follows:

A. **Population:** as described by the inclusion/exclusion criteria given in Section 5 and further by analysis population in Section 9.3

B. **Variable:** change from baseline in 24h cough count after 12 weeks of intervention

C. **Treatment:** BAY 1817080 or placebo

D. **Intercurrent events**:

   a. early discontinuation of study intervention: use data until discontinuation (while on treatment strategy)

   b. non-compliance with study intervention: use data until non-compliance (while on treatment strategy)

E. **Population-level summary:** estimated mean of change from baseline in the logarithm of average hourly cough count by intervention group

The estimator used for this estimand is described in detail in Section 9.4.2.

4. Study Design

4.1 Overall Design

Study design summary: Randomized, double-blind, parallel group, Phase 2b dose-finding, efficacy and safety study of 12-week twice daily oral administration of BAY 1817080 compared to placebo in patients with RUCC.

Intervention group:	Parallel
Study duration:	Approximately 18 weeks
Intervention duration:	12 weeks
Study Periods:	Pre-intervention period (screening & randomization), Intervention period, and Safety follow-up period
Diagnosis group:	Patients with RUCC

The study population consists of participants with a cough that has lasted for at least 12 months (unresponsive to treatment options) with a diagnosis of refractory chronic cough and/or idiopathic (unexplained) chronic cough and with persistent cough for at least the last 8 weeks before screening.

4.1.1 Pre-Intervention Period

Written informed consent form must be obtained before any study related activities are performed. After providing the written informed consent, participants will undergo a screening evaluation to determine their eligibility. The screening evaluation will take place on Day -14 before Visit 2.

The screening of each participant has to be recorded in the IWRS system. To assure timely drug supply to each study site, the recording of randomization must be completed at least 1 day but not later than 4 days after Visit 1 (before Visit 2). The recording of randomization in IWRS of a participant who is eligible for intervention must be repeated on the day of the planned start of intervention. This will be considered confirmation of randomization and will trigger the notification to the site about the study intervention assignment.

Following screening, eligible participants will be randomized to one of four parallel intervention groups of BAY 1817080.

4.1.2 Intervention Period

After randomization, each participant will receive one of three doses of BAY 1817080 or placebo administered orally with or without food, twice daily over the course of 12 weeks with an interval of 12 hours.

4.1.3 Post-Intervention Period

After last intake of study intervention, participants will enter an observational safety follow-up period of 30±5 days. During this period, AEs will continue to be collected. At the end of this observational period, a safety follow-up (SFU) visit will be performed at site.

For an overview of activities and procedures to be performed at each visit, see SoA.

4.2 Scientific Rationale for Study Design

This Phase 2b dose-finding study with BAY 1817080 administered twice daily for 12 weeks will provide further data to support the determination of a dose with the highest potential for efficacy and with optimal risk-benefit profile for patients with RUCC. Twelve weeks on intervention is considered sufficiently long to identify optimal dose and explore whether BAY 1817080 has superior efficacy over placebo.

The inclusion of a placebo-controlled arm is regarded as fundamental to minimize bias on the part of participants and investigators. Randomization is designed to prevent assignment or selection bias. RUCC is a condition with a known behavioral component, potentially susceptible to a placebo effect.

Rationale for the primary efficacy endpoints

Cough is associated with significant physical and psychological morbidity (14). In the research environment, the ability to measure relevant cough parameters is necessary for understanding its mechanism and developing new treatments (15).

Coughing can be assessed either from the perspective of the patient or from that of the clinician or researcher. Both approaches are very useful and complementary, therefore combined subjective and objective assessment is necessary for more comprehensive evaluation. An objective measure of cough is of use in clinical practice, clinical research and the assessment of novel therapies. It permits validation of the presence of cough, grading of severity and monitoring of response to treatment (16).

The assessment of cough severity is considered the most important parameter for evaluating the efficacy of therapy and it can be measured by symptom severity, frequency, intensity and impact on quality of life, with the validated tools available. There is a general consensus that cough frequency monitoring is the gold standard for the objective assessment of cough and it has been increasingly used as primary endpoint in clinical trials, although there is currently no standardized method for measuring cough frequency (3).

An objective measure of cough would permit validation of the presence of cough, grading of severity and monitoring of responses to therapeutic intervention. Therefore, our primary efficacy endpoint is the assessment of change from baseline in 24-hour cough count (measured by cough recording digital wearable monitoring device) after 12 weeks of intervention.

4.3 Justification for Dose

In this study, the doses were selected based on the following:

- The selected dose should result in sufficiently high exposures that block the target to an extent which allows to conclusively determine the optimal dose to be tested in subsequent confirmatory Phase 3 trials in RUCC.
- The safety/ tolerability profile based on clinical evidence gathered to date will ensure participants' safety during trial participation and reduce the risk of early discontinuations due to adverse events (AEs) or perceived lack of efficacy.

For BAY 1817080, the above-mentioned criteria are fulfilled for the selected doses of 75 and 150 mg BID[2]:

- Based on current dose predictions from preclinical studies and data from the proof of concept study in patients with refractory and/or unexplained chronic cough (study 18184), the lowest fully effective dose was observed at a dose of 200 mg BID with formulation A[3]. Exposures after dosing of 200 mg BID with formulation A correspond to exposures expected with ~75 mg BID with formulation B. In this study, formulation B is used.
- The doses of 25, 75 and 150 mg BID were chosen in order to allow investigating the full dose response in RUCC, i.e., testing one lower, partially effective dose of 25 mg and one higher, also fully effective dose of 150 mg BID (formulation B). The doses of 25, 75 and 150 mg BID of formulation B are expected to be similar to the doses of 50 mg, 200 mg and 750 mg of formulation A previously tested in Phase 2a (see Figure 4–1).
- Participants are recommended to take the tablets at approximately the same time each day with or without food. Tablets are not to be broken, halved or crushed; they should be swallowed as a complete unit with water (see Figure 4–1 and the latest available version of the IB for further details).
- In summary, expected exposures after administration of 25, 75 and 150 mg BID of BAY 1817080 are believed to be sufficient to conclusively investigate the dose response in patients with RUCC.
- In study 18184, the highest exposure (after multiple doses of 750 mg of formulation A) was found to be well tolerated and safe (see the latest available version of the IB for further details)[4]. 750 mg BID of formulation A translates into approximately 150 mg BID of formulation B. Accordingly, exposures following administration of 25, 75

---

2 Formulation B CCI [redacted] [see the latest available version of the IB for further details])

3 Clinical proof of target engagement is derived from the proof of concept study with BAY 1817080 in patients with refractory and/or unexplained chronic cough (study 18184; see the latest available version of the IB). For patients who had received the maximum technically feasible dose of 750 mg BID or the next lower dose of 200 mg BID, awake cough counts were reduced on top of placebo by 26.1% and 24.4%, respectively.

4 Patients who had received the maximum technically feasible dose of 750 mg BID or the next lower dose of 200 mg BID experienced taste-related adverse events at a rate of 15.4% and 20.5%, respectively. Such AEs were also observed after administration of a different P2X3 antagonist (gefapixant) (12).

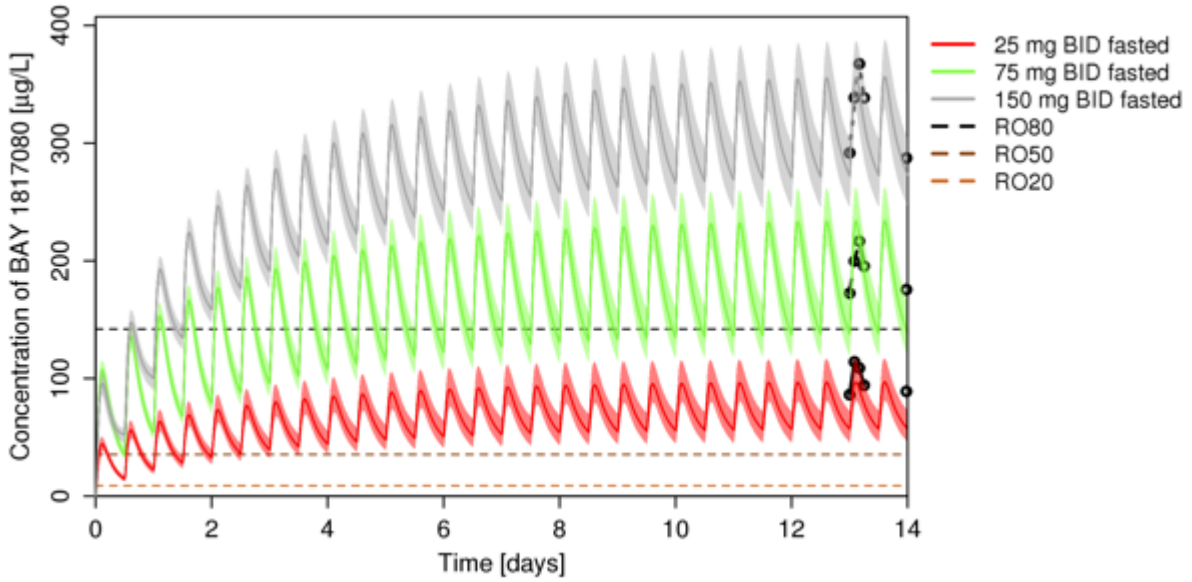
and 150 mg BID of formulation B are expected to be similar to the concentrations covered in the multiple dose study 18184 (see the latest available version of the IB and Figure 4–1 below; applies to both fasted and fed state).

- Additionally, in study 19519, a 400 mg single dose of formulation B was found to be safe.

Therefore, there are no anticipated safety concerns with the selected doses of 25, 75 and 150 mg BID (formulation B) of BAY 1817080 in study 20393. Tolerability is expected to facilitate completion of the study by the required number of participants and accordingly interpretation of study results (i.e., rate of early discontinuations within expectations).

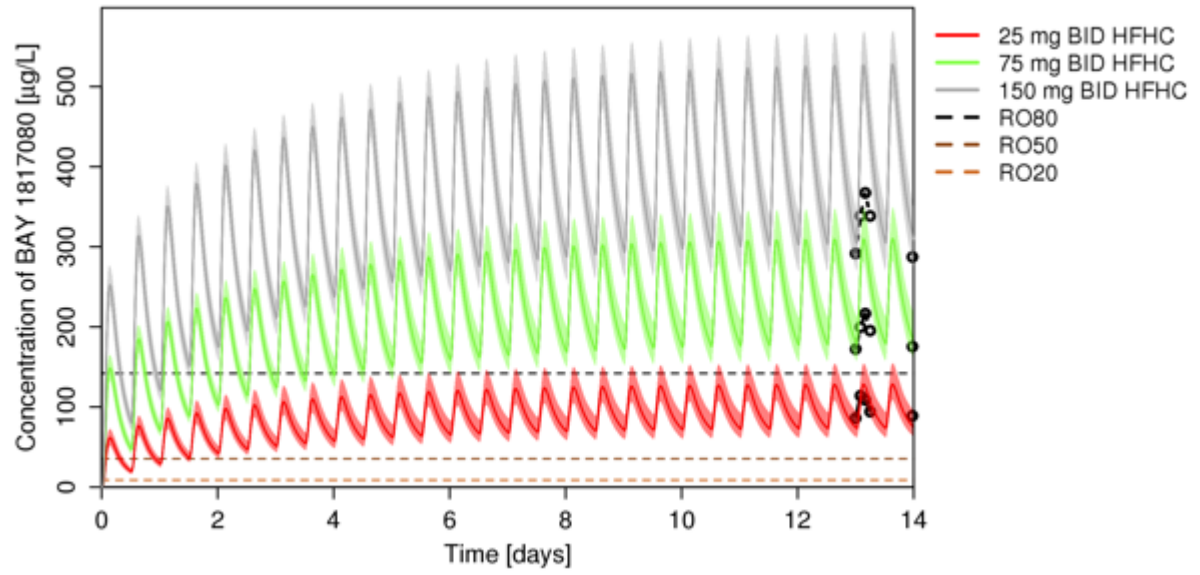
Figure 4–1: Model-Based Predicted Average Concentrations After Administration of 25, 75 and 150 mg BID of BAY 1817080 Formulation B

A)



Model-based predicted average concentrations (including 95% confidence interval) after multiple dose administration (BID) of 25 mg, 75 mg and 150 mg of BAY 1817080 formulation B given fasted, in comparison to the geometric mean concentrations (steady-state, BID) observed in study 18184 Part 2 with 50 mg, 200 mg and 750 mg of formulation A (black circles & black lines). 75 mg: based on 25 mg fasted model.

B)



Model-based predicted average concentrations (including 95% confidence interval) after multiple dose administration (BID) of 25 mg, 75 mg and 150 mg of BAY 1817080 formulation B given fed (high fat, high calorie meal), in comparison to the geometric mean concentrations (steady-state, BID) observed in study 18184 Part 2 with 50 mg, 200 mg and 750 mg of formulation A (black circles & black lines). 75 mg: based on 100 mg fed model.

Abbreviations: BID = bis in die (twice daily); HFHC = high fat, high calorie; RO = receptor occupancy

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit (SFU).

The primary completion is defined as the date of Visit 6 of the last participant for the primary outcome.

The end of the study is defined as the date of the last visit (SFU) of the last participant in the trial globally.

5. Study Population

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Adults ≥ 18 years of age at the time of signing the informed consent.
2. A cough that has lasted for at least 12 months (unresponsive to treatment options) with a diagnosis of refractory chronic cough and/or idiopathic (unexplained) chronic cough.
3. Persistent cough for at least the last 8 weeks before screening.
4. Cough severity as measured by VAS ≥40 scale units at screening.
5. Women of childbearing potential must agree to use acceptable effective or highly effective birth control methods during the study and for at least 30 days after the last dose. For more details on contraception (and highly effective birth control methods), see Section 10.4.
6. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

RUCC-related Medical Conditions

1. Smoking history within the last 12 months before screening (all forms of smoking, including e-cigarettes, cannabis and others), and any former smoker with more than 20 pack-years.
2. Ongoing or previous exposure to inhalational toxic fumes (e.g., ammonia, chlorine, nitrogen dioxide, phosgene and sulfur dioxide) within the last 12 months before screening.
3. Chest radiograph or CT within the last 24 months before screening and subsequent to the onset of chronic cough with presence of any obvious lung disease that could be responsible or contributing for the cough (e.g., bronchiectasis, cavitary lesions, interstitial pulmonary fibrosis, pneumothorax, pleural disease, unstable rib fracture, tuberculosis).

4. Forced expiratory volume in 1 second (FEV1)/ Forced vital capacity (FVC) ratio < 60% or a history of frequent exacerbations of chronic obstructive pulmonary disease (COPD).
5. Respiratory tract infection within 4 weeks before screening.
6. History of chronic bronchitis.
7. Active state of massive hemoptysis[5] or pulmonary hemorrhage, including those events managed by bronchial artery embolization or any history of bronchial artery embolization or massive hemoptysis within 3 months prior to screening.

Hepatic-related criteria

8. Moderate-to-severe hepatic impairment defined as Child-Pugh Class B or C.
9. ALT >2xULN, or AST >2xULN, or total bilirubin greater than ULN, or alkaline phosphatase (AP) >2x ULN, or INR greater than ULN (unless related to anticoagulation treatment).

Renal-related criteria

10. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 calculated by Modification of Diet in Renal Disease (MDRD) formula.

    Different eGFR formulas will be used for participants enrolled at sites in Japan in this study (for more details, see Section 10.6).

General Medical Conditions

11. Systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg at screening visit.
12. Any other diseases or conditions that according to the investigator can compromise the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study intervention (e.g., chronic bowel disease, Crohn's disease and ulcerative colitis).
13. Esophageal achalasia.
14. Any serious or unstable diseases or conditions including psychiatric disorders that might interfere with the conduct of the study or the interpretation of the results.
15. Concurrent malignancy or history of cancer (exception of basal cell or squamous cell carcinoma of the skin) within the last 5 years prior to screening.

Prior/Concomitant Therapy

16. Intention to start new treatment for RUCC during the study.
17. Intake of prohibited prior or concomitant therapy as specified in Section 6.5.

---

[5] Massive hemoptysis is a medical emergency defined as any degree of hemoptysis causing life-threatening clinical consequences such as but not limited to respiratory failure from airway obstruction, hypoxemia requiring mechanical ventilation, transfusion, hypotension, etc. (17)

COVID-19 related criteria

18. Positive SARS-CoV-2 virus RNA and/or serology IgG tests at screening visit.

Other exclusions

19. Body mass index (BMI) > 40 kg/m^2.
20. Hypersensitivity to any ingredient of the study intervention (see the latest available version of the IB).
21. Wish for pregnancy during the study, current pregnancy or lactation.
22. Major surgery scheduled during the study period.
23. Inability to cooperate with the study procedures for any reason, including the following examples: language comprehension, inability to get to the study site.
24. Abuse of alcohol or medicines, or use of recreational/illicit drugs, as evaluated by the investigator.
25. Previous assignment to treatment (e.g., randomization) during this study.
26. Simultaneous participation in another clinical trial with investigational medicinal product(s).
27. Participation in another P2X3 trial within 3 months prior to screening.
28. Close affiliation with the investigational site; e.g., a close relative of the investigator, dependent person (e.g., employee or student of investigational site, or sponsor's staff).
29. Otherwise vulnerable patients. Patients who are in custody by order of an authority or a court of law.

5.3 Lifestyle Considerations

All forms of smoking, including e-cigarettes, cannabis and others, are not allowed. Use of tobacco products will not be allowed from screening until after the final SFU visit.

As a precautionary measure, excessive exposure to sunlight should be avoided during the intervention period. Participants will be advised to use conventional ultraviolet (UV) sunscreens, to avoid prolonged sunbathing especially when traveling to a different geographical area with greater sunshine, to avoid the use of solarium and also to wear sunglasses if exposed to direct or excessive sunlight (see Section 2.3.3.6).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes

- Demography,
- Reason for screen failure,
- Eligibility criteria, and
- Date of last visit.

A participant who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure".

Re-starting the defined set of screening procedures to enable the "screening failure" patient's participation at a later time point is not allowed.

Dropout

A participant who discontinues study participation prematurely for any reason is defined as a "dropout" if the participant has already been randomized to study intervention. Dropouts will not be replaced.

6. Study Intervention

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

6.1 Study Interventions Administered

- Each participant will be randomized to receive one of three oral doses of BAY 1817080 or placebo, administered twice daily
- Participants should be instructed to take the morning dose of study intervention at approximately the same time of day, every day over the course of 12 weeks. The interval between the application of the morning and the evening dose should be with an interval of approximately 12 hours.
- The morning dose should be taken at the site on the second day of Visit 6 (see also Section 8.5)
- Tablets are not to be broken, halved or crushed; they should be swallowed as a complete unit with water.
- Tablets can be taken with or without food. See Section 8.5 for detailed instructions regarding recording of the drug intake and the food intake before or after the drug intake in relation to blood sampling for PK.
- Participants will have to confirm the tablet intake twice per day by reporting this on the handheld device. In addition, the time of the tablet intake will be collected.
- If a dose of study intervention has been missed:
    - If ≤ 6 hours has passed since the dose was due, it should be taken immediately
    - If > 6 hours have passed since the dose was due, the dose should be skipped and the next dose should be taken according to the regular schedule.

Table 6–1: Study Interventions Administered

	BAY 1817080	Placebo
Intervention Name	BAY 1817080	Placebo for BAY 1817080
Type	Drug	Placebo
Dose formulation	Tablet	Tablet
Unit dose strengths	25 mg and 100 mg	NA (Placebo for BAY 1817080 25 mg and BAY 1817080 100 mg)
Dosage Levels	25 mg or 75 mg or 150 mg BID	NA (Placebo)
Route of Administration	Oral	Oral
Packaging and Labeling	Tablets will be provided in blisters. Study intervention will be labeled as required per country requirement.	

Abbreviations: BID = twice daily; NA = not applicable

6.1.1 Medical Device

A commercially available cough recording device (VitaloJAK™; Vitalograph GmbH) will be used for the 24-hour ambulatory measurements. For further information, see the handling instruction and the instruction manual as provided with the device by the legal manufacturer.

6.2 Preparation/Handling/Storage/Accountability

The investigator or designee must confirm that appropriate temperature conditions, if applicable, have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply or administer the study intervention.

All study interventions 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 site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Site File.

Study interventions will be dispensed at the visits summarized in SoA. Returned study interventions must not be re-dispensed to the participants.

6.3 Measures to Minimize Bias: Randomization and Blinding

Participants will be identified by a unique participant number with 9 digits once the ICFs are signed. The first 5 digits will identify the country and study site, the last 4 digits are assigned to the participant of the specific site in increasing order.

Following the screening visit (Visit 1), all participants who meet all eligibility criteria will be centrally randomized in a 1:1:1:1 allocation ratio and stratified by region (Japan, Europe [Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Slovakia, Spain, United Kingdom], ROW [Argentina, Australia, Canada, Russian Federation, Taiwan, Turkey, United States]) to receive either BAY 1817080 or placebo by using IWRS.

Once a randomization number has been assigned, it must not be re-assigned.

To accomplish randomization assignments, a computer-generated randomization list will be prepared by Randomization Management at the study sponsor. The randomization list is provided to the IWRS vendor. Before the study is initiated, the login information & directions for the IWRS will be provided to each site.

After randomization, participant, investigator and sponsor will be blinded for the intervention participant receives.

To maintain blinding, tablets containing BAY 1817080 and corresponding placebo are identical in appearance (size, color, shape). BAY 1817080 25 mg, 75 mg, and 150 mg, and matching placebos will be packaged in blisters labeled with a unique number. For regulatory reporting purposes, drug safety personnel of the sponsor are permitted to unblind individual cases. In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reaction (SUSAR), the randomization code of the participant will usually be unblinded before reporting to the health authorities.

Bioanalytical staff will be unblinded according to the corresponding Bayer standard operating procedure (SOP). Pharmacometrics staff may also be unblinded according to Bayer SOPs. Pharmacokinetic (PK) and exposure-response analysis might be performed using population approaches (popPK and popPK/PD, e.g., by non-linear mixed effect modeling). Analysis and report will be done under a separate cover. This evaluation might be started prior to database lock. If this is applicable, appropriate measures will be taken to maintain blinding of the study team, e.g., data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

Emergency unblinding can only be performed in the IWRS system. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a participant's intervention assignment is warranted when knowledge of the actual intervention is absolutely essential for further medical management of the participant. If the investigator is unavailable, and a treating physician not associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the study specific emergency medical advice 24 hours/7-day service (country-specific emergency contact information provided in the participant card). Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable. The actual allocation must NOT be disclosed to the participant and/or other study personnel, including monitors, or sponsors staff; nor should there be any written or verbal disclosure of the code in any of the corresponding participant documents.

6.4 Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

To monitor compliance, the investigator will be required to document intervention dispensing and return for each participant. The date of dispensing the study intervention to the participant will be documented.

Study intervention will be dispensed according to the schedule provided in SoA. Participants should be instructed to bring all unused study intervention and empty packages at every scheduled/unscheduled visit for accountability purposes. Any discrepancies between actual and expected amount of returned study intervention must be discussed with the participant at the time of the visit, and any explanation must be documented in the source records.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit.

6.5 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment up to 12 weeks prior to screening or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

A list of prohibited prior and concomitant medications, along with the timeframe is provided in Table 6–2.

Medications that are allowed only if the participant is on stable treatment (prior to and at enrollment) are described in Table 6–3. Other treatment considerations are described below.

Table 6–2: Prohibited Prior and Concomitant Therapy

Therapy	Timeframe
Angiotensin converting enzyme inhibitor (ACEI)	From 12 weeks prior to screening until EoI
Opioids, including codeine	From 2 weeks prior to screening until EoI
Digoxin	From 2 weeks prior to screening until 2 weeks after EoI
Dabigatran	From 2 weeks prior to screening until 2 weeks after EoI
Apixaban	From 2 weeks prior to screening until 2 weeks after EoI
Edoxaban	From 2 weeks prior to screening until 2 weeks after EoI
Gabapentin/pregabalin (for chronic cough)	From 2 weeks prior to screening until EoI
Tricyclic antidepressants (i.e., amitriptyline, nortriptyline) (indication RUCC)	From 4 weeks prior to screening until EoI
Interferon alpha-2b and alpha-2a	From 2 weeks prior to screening until EoI
Mycophenolate mofetil	From 1 week prior to screening until EoI
Methotrexate	From 4 weeks prior to screening until EoI
Ribavirin	From 2 weeks prior to screening until EoI
Non-narcotic cough medicine (including over-the-counter and herbal)	From 1 week prior to screening until EoI
Strong cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors including: • antivirals (e.g., viekira pak, telaprevir, boceprevir), • protease inhibitors (e.g., ritonavir, lopinavir, indinavir, nelfinavir, saquinavir) • antifungals (e.g., itraconazole, voriconazole, posaconazole) • antibiotics (e.g., clarithromycin, telithromycin) grapefruit and any grapefruit containing food products (e.g., grapefruit juice)	From 2 weeks prior to screening until EoI
Strong CYP3A4 inducers, e.g., rifampicin, carbamazepine, phenytoin, St John´s Wort	From 2 weeks prior to screening until EoI
Non-drug treatment for RUCC	
Speech Therapy	From 4 weeks prior to screening until EoI
Chinese medicine	From 4 weeks prior to screening until EoI

Abbreviations: EoI = end of intervention; RUCC = refractory and/or unexplained chronic cough

A list of permitted medication only on stable dose is provided in Table 6–3. It is not permitted to change the daily dose of these medications within the timeframe described below (prior to and screening).

Table 6–3: Medication Permitted on Stable Dose

Therapy	Timeframe of stable treatment
Benzodiazepines	From 4 weeks prior to screening until EoI
Paroxetine	From 4 weeks prior to screening until EoI
Baclofen	From 4 weeks prior to screening until EoI
Memantine	From 4 weeks prior to screening until EoI
Azithromycin and erythromycin	From 4 weeks prior to screening until EoI
Antihistamines (Chlorphenamine) for chronic cough	From 4 weeks prior to screening until EoI
Gabapentin/pregabalin (other indications e.g., diabetic neuropathy, neuropathic pain)	From 4 weeks prior to screening until EoI
Tricyclic antidepressants (i.e., amitriptyline, nortriptyline) (other indications)	From 4 weeks prior to screening until EoI
Asthma medications (e.g., inhaled corticosteroids, leukotriene modifiers, log-acting beta agonists, theophylline)	From 4 weeks prior to screening until EoI
Proton-pump inhibitors	From 8 weeks prior to screening until EoI

Abbreviations: EoI = end of intervention

Dose changes in these medications should be avoided during the study. Dose changes considered clinically necessary by the investigator need to be documented in the eCRF and the clinical condition / diagnosis that led to this dose modification should be captured as AE.

6.5.1 Other Treatment Considerations

Apixaban, dabigatran, edoxaban, digoxin: prohibited within the last 2 weeks prior to screening visit and until 2 weeks after end of intervention period of this study.

Based on preclinical data, an increase in exposure of drugs that are sensitive substrates of OATP1B1/1B3, P-gp or BCRP during co-administration of BAY 1817080 due to inhibition of those transporters by BAY 1817080 cannot be excluded.

- Typical OATP1B1, OATP1B3, BCRP or P-gp substrates include but are not limited to the following: fexofenadine, sulfasalazine, rosuvastatin, atorvastatin, cerivastatin, glyburide, pravastatin, repaglinide, simvastatin.
- Participants receiving a combination of BAY 1817080 and OATP1B1/1B3, BCRP and P-gp substrates should be closely monitored for signs and symptoms of adverse events due to increased exposure of co-administered OATP1B1/1B3, BCRP or P-gp substrates. Dose modification of sensitive OATP1B1/1B3, BCRP or P-gp substrates should be considered based on the prescriber information or such compounds should be avoided.

A clinical DDI study investigating the effect of BAY 1817080 on the sensitive OATP1B1/1B3 and BCRP substrate rosuvastatin is ongoing.

According to the risk assessment based on the FDA Drug Development and Drug Interactions (DDI) guidance (18), the potential increase in exposure (AUC) due to inhibition of OATP1B1, the transporter with the lowest measured IC_{50} is estimated to be up to 2.85-fold with the highest dose of 150 mg BID of BAY 1817080 (simulated steady state exposure of formulation B was used for DDI predictions). The parameters used for this calculation are

entirely based on IC_{50} values determined in *in vitro* assays reflecting the maximum possible effect. The clinical relevant interaction will be assessed in the ongoing clinical DDI study investigating the effect of BAY 1817080 on the sensitive OATP1B1/1B3 and BCRP substrate rosuvastatin. Please refer to the current version of the IB for further information.

Additional information regarding other OATP1B1, OATP1B3, BCRP and P-p substrates can be found in Table 5-1 of the FDA DDI guidance (19).

Ketoconazole and other triazole antifungal drugs are allowed for topical/local use (including vaginal application) at any time during the study.

Occasional intake of proton-pump inhibitors as treatment for concomitant AE, at the discretion of the investigator is allowed, but not recommended. Alternative treatment options are strongly suggested to be considered.

6.6 Dose Modification

Dose modification is not allowed within the study.

6.7 Intervention after the End of the Study

Participants completing the intervention period will not be given further access to study intervention. The investigator will decide in consultation with the individual participant if additional treatment is required and choose from existing treatment options.

It will be up to the investigators discretion to provide follow-up medical care for all participants who complete the study or who are prematurely withdrawn from the study or refer them for appropriate ongoing care as required.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Unnecessary withdrawal of participants from the study should be avoided and all efforts should be taken to motivate participants to adhere to all study procedures until the end of the trial.

In case a participant premature discontinues the study intervention, the participant will remain in the study to be evaluated for the procedures planned at EoI and SFU visits before the participant leaves the study. See the SoA for data to be collected at the time of discontinuation of study intervention.

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Such events are expected to be rare.

If study intervention is discontinued, a participant who is still in the intervention period should have the EoI visit (Visit 6) assessments performed as soon as possible. Following Visit 6, the participant continues to the follow-up period and the end of study visit (i.e., the SFU visit) assessments thereafter according to the SoA.

Participants *must* discontinue study intervention if any of the following occurs:

- In the investigator's opinion, continuation of the study intervention would be harmful to the participant's well-being
- Liver safety-related discontinuation criteria are met as described in Table 7–1.
- Pregnancy (see Sections 8.3.5 and 10.4).

Table 7–1: Liver Safety-Related Monitoring and Discontinuation Criteria

Lab result	Measures
ALT or AST >3 x ULN	• Repeat testing of ALT, AST and TBL 2-3 times a week • Withdraw study intervention if the participant cannot come for a repeat testing* • 'Close observation' as defined in Section 8.3.6
ALT or AST >3 x ULN **and** TBL >2 x ULN	Withdraw study intervention and initiate close observation as outlined in Section 8.3.6
ALT or AST >3 x ULN **and** INR >1.5 x ULN**	Withdraw study intervention and initiate close observation as outlined in Section 8.3.6
ALT or AST > 3 ULN with appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)	Withdraw study intervention and initiate close observation as outlined in Section 8.3.6
ALT or AST >5 x ULN for more than 2 weeks	Withdraw study intervention and initiate close observation as outlined in Section 8.3.6
ALT or AST >8 x ULN	Withdraw study intervention and initiate close observation as outlined in Section 8.3.6

*i.e., in case no visit for a repeat testing could be arranged within a reasonable time frame despite efforts to contact the participant

**Relevant only if the participant is not on Vitamin K antagonist or heparin

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio, TBL = total bilirubin, ULN = upper limit of normal (all referring to serum)

In participants fulfilling one of the criteria listed in Table 7–1, investigators and participants should be alerted regarding non-specific symptoms which may be associated with liver dysfunction, including anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting, malaise, jaundice, fever, and rash. Information on these symptoms should be asked for in case of abnormal liver laboratory values (see Table 7–1) or any other suspicion of liver dysfunction. The study participants should be reminded to contact the study site immediately, if they are concerned about such symptoms, and unscheduled liver laboratory assessments should be considered.

A close observation has to be initiated if any of the criteria listed in Table 7–1 occurs.

7.1.1 Rechallenge

Study intervention may be restarted after a temporary interruption if deemed clinically appropriate by the investigator in collaboration with the Bayer Medical Monitor.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or he/she may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The participant will not suffer any disadvantage as a result. Withdrawals from the study are expected to be rare.
- If a participant becomes SARS-CoV-2 virus RNA test positive while on study, the investigator will have to decide whether staying in the study is compatible with participant and site personnel safety and wellbeing. The decision should also take into account possible interaction between the test drug and potential antiviral medication (for details on concomitant therapy see Section 6.5).
- At the time of withdrawal from the study, the participant must discontinue study intervention *and* complete the following visits as soon as possible:
    - For withdrawal during intervention phase, the participant should undergo assessments scheduled for the end of intervention visit (Visit 6) and return supplies.
    - In addition, the participant should undergo the assessments scheduled for end of study visit (the SFU visit).
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Data already captured at the time of withdrawal will not be removed.

7.3 Lost to Follow Up

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

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

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

No screening procedures may be performed unless written informed consent has been obtained. If the (first) screening procedures already start on the same day (same date) as the participant signs the ICF, confirmation that ICF was signed prior to any screening procedures being initiated, must be recorded in the source documents.

Information on smoking history and a detailed history of symptoms and complications as a result of cough (type, onset, duration and time of resolution) will be recorded at screening visit via a series of questions reflected on individual eCRF page as part of the participant's medical history. Worsening of any of the conditions listed on the aforementioned eCRF page or their first occurrence after signing the informed consent will be recorded as AEs.

8.1 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (see Section 1.3).

8.1.1 Cough Count Measurement

Objective 24-hour cough monitoring will be performed with the VitaloJAK cough recorder (VitaloJAK, Vitalograph), a non-invasive, battery operated and custom-built validated recording device and microphone intended to acquire, record and store ambulatory cough sounds from participants for 24 hours at six time points (see the SoA). Briefly, this consists of a digital data logger recording sounds at a sample rate of 8 kHz, with 16-bit resolution and in WAV format, which is a commonly used uncompressed sound file format. Recordings will be transferred to a personal computer; silences and background noise will be removed by using validated, custom-written software, and cough sounds will be counted by using an audio editing package (Vitalograph). The number of coughs will be expressed as coughs per hour and added up to give a cough count for a 24-hour period. Cough monitoring with the VitaloJAK recorder will be started at approximately the same time of day on each of the assessment days.

8.1.2 Electronic Patient Reported Outcomes (ePROs)

Patient reported outcomes (PROs) are self-administered questionnaires to be completed by the study participants themselves. All questionnaires will be available in the participant's local language.

For standardization purposes, in this study all PROs will be collected using electronic devices: either (e)PRO/electronic handheld device to be responded to at home for daily entries or tablet devices for entries at the study site during the entire study duration.

PROs collected daily on the handheld device

The following PROs will be collected daily on the handheld device in the following sequence:

- SCCD
- Severity of Cough VAS

The estimated time for completion is approximately 5 minutes, calculated using a conservative approach (30 seconds per item).

PROs collected during study site visits at the study site using a tablet device:

The following PROs will be collected on the tablet device in the following sequence:

- LCQ
- PGI-S
- PGI-C
- EQ-5D-5L

The estimated time for completion is approximately 6 minutes, calculated using a conservative approach (30 seconds per item).

Dispensation of the handheld device, data entry into the handheld device and the tablet device and transmission:

Following training on the use of the handheld device and the tablet device during Visit 1, the participants will be asked to confirm their understanding on the use of the devices and the completion of the PROs before the devices are activated and dispensed to the study participants for recording.

The specific time window for data entry into the handheld device is PRO-specifically technically regulated and alarms will be set as appropriate to remind the study participant to complete the SCCD, the Cough Severity VAS (and the study intervention intake), respectively. The study participants will be asked to fill in the daily (every day at the same time). Alarms will be set to remind the study participants to complete the PROs at the same time every day. This alarm will be set at a certain time per day and will sound in general only, if the PROs have not already been completed.

The PROs on the tablet device will be responded to by the study participants at the selected visits (see SoA) prior to any other assessment and procedures.

Training of study participants:

Study participants will be educated regarding the importance of their in-time correct completion of the ePROs during the study. Standardized technical training for the use of the handheld device and the tablet device during the screening visit and ongoing technical support during the entire study duration will be provided by the study site staff to prevent missing data entry to the extent possible. Beyond this technical support, no other help should be given to study participants regarding the completion of the ePROs and the study participant will be instructed to complete the ePROs on their own, in a quiet place in one sitting at the pre-specified time points, following the instructions on the tablet device, without any input from others.

Training of and by site staff, 24-hour help desk

Study site staff will be instructed to explain to the study participants at each visit the importance of completing the records on the handheld and tablet devices. The study site staff will be trained regarding the use of the handheld device, and in resolving technical issues with

the handheld device and the tablet device. The study site staff will provide a standardized technical training on the handling of the handheld-device and the tablet device to the study participants during the screening visit and will assist the study participants in case of any technical queries during the entire study duration.

In addition to the technical support by the study site staff, a 24-hour help desk by the ePRO provider will be available during the entire study duration to respond urgent technical questions of the site staff.

Measures to prevent missing data entry

In case a warning due to missing data entry is received at the study site, the study site staff will directly contact the study participant immediately and ask for reasons for failure in data entry and transfer. The study site staff will remind the study participant again regarding the importance of the daily records.

The handheld device will be returned to the site upon study participant discontinuing or completing the study.

8.1.2.1 Severity of Chronic Cough Diary (SCCD)

Study participants' assessment of frequency, severity of cough, disruption due to cough and disruptions of sleep will be recorded electronically every day from screening until the end of the intervention period using the SCCD.

The SCCD is a novel 14-item PRO questionnaire, asking the participant to assess experiences with their cough during the past 24 hours. Study participants will rate the frequency (items 1-4), severity (items 5-8), disruptions due to cough (items 9-11 and 14) and disruptions of sleep (items 12-13) using verbal rating scales (VRS) and are asked to enter their daily assessments directly into the handheld device at home. The completion of the SCCD takes approximately 5 minutes.

The daily recording of the SCCD will start at Visit 1 and will be continued daily until the SFU visit or at early termination for those study participants discontinuing the study before completion.

SCCD scores will be calculated based on study participants' responses to single items.

The SCCD is a PRO, which has been newly developed by Bayer. The SCCD underwent cognitive interviews (CIs) confirming the content validity, the ease of comprehension, interpretation and completion prior to initiation of this study. Psychometric and other measurement properties of the SCCD are planned to be assessed using data from this trial. Results from the CIs and the psychometric analyses are aimed to confirm the appropriateness of the instrument for use in clinical Phase 3 in potential support of label claims.

Training and instructions will be provided to participants in terms of how to complete the questionnaire.

8.1.2.2 Cough Severity Visual Analog Scale

Study participant assessment of cough severity will be recorded electronically daily using the Cough Severity Visual Analogue Scale (VAS).

The Cough Severity VAS is a single item instrument, asking the study participant to assess the severity of his/her cough using a 0-100 VAS. This is a vertically oriented line ordered from 0–100, on which the study participants indicate the severity of their cough by crossing the line at the point that that best reflected the perception of the severity of their cough on

their handheld device. The completion of the Cough Severity VAS will take less than 1 minute.

The daily recording of the Cough Severity VAS will start at Visit 1 and will be continued daily until the SFU visit or at early termination for those study participants discontinuing the study before completion.

The Cough Severity VAS response option is known for its simplicity and practicality and is commonly used in clinical research for the measurement of a variety of clinical phenomena (20), including for the assessment of cough (16). The scale response range is from ("No Cough") to 100 ("Extremely Severe Cough"). A change of 17 scale units on a VAS has been reported to be perceived as important to subjects with acute cough (21). Clinical trial endpoints evaluating treatments for chronic cough include an endpoint of '≥ 30 scale units Reduction From Baseline in Cough Severity Visual Analog Scale (VAS) Score'(22).

In this trial, the Cough Severity VAS will assess key secondary and other efficacy endpoints. Scores from the Cough Severity VAS will also be used to investigate psychometric properties of the SCCD.

8.1.2.3 Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C)

PGI-S and PGI-C will be assessed on the tablet device at predefined visits according to the SoA or at earlier termination for those study participants discontinuing the study before completion.

PGI-S

Study participants rate the severity of cough using the PGI-S scale experienced at the time point of the assessment (no recall period).

The PGI-S is a single item instrument. Study participants respond to the PGI-S using a 5-point verbal rating scale: a score of 0 = "No cough", 1 = "Very mild", 2 = "Mild", 3 = "Moderate", 4 = "Severe", 5 = "Very severe" and will enter their assessment on a tablet device during study visits. The PGI-S is being included in the trial as a reference measure for assessment of psychometric and other measurement properties of the newly developed SCCD.

PGI-C

Study participants rate the change in the severity of their cough using the PGI-C scale since starting study intervention at the different assessment time points respectively. Study participants respond using a 7-point verbal rating scale: a score of 0 = "Very much better", 1 = "Much better", 2 = "A little better", 3 = "No change", 4 = "A little worse", 5 = "Much worse" and 6 = "Very much worse". The PGI-C is being included in the trial as a reference measure for assessment of psychometric and other measurement properties of the newly developed SCCD.

8.1.2.4 Leicester Cough Questionnaire

Study participants assessment of health related quality of life will be recorded electronically using the Leicester Cough Questionnaire LCQ (23).

The LCQ is a 19-item instrument that asks about the impact of chronic cough on various aspects of participants' lives using a recall period of two weeks. The 8 items: 1, 2, 3, 9, 10,

11, 14, 15 build the physical domain. 7 items: 4, 5, 6, 12, 13, 16, 17 build the psychological domain. Further 4 items: 7, 8, 18 and 19 build the social domain.

Study participants respond to the items using a 7-point Likert scale from 1 (all of the time) to 7 (none of the time) and will enter their assessments on a tablet device during study visits according to the SoA or at earlier termination for those study participants discontinuing the study before completion. Completion of the LCQ takes approximately five minutes.

The LCQ total score is calculated as a mean score for each of the three domains ranging from 1 to 7, with the LCQ total score ranging from 3 to 21. A clinically significant improvement in cough-specific quality of life (QoL), is indicated by a ≥1.3-point increase in the LCQ total score from baseline (24).

In this trial, the LCQ will assess key secondary and other efficacy endpoints. Scores from the LCQ will also be used to investigate psychometric properties of the SCCD. The LCQ version used in this trial is © 2001. S. Birring, UK.

8.1.2.5 EQ-5D-5L

The EQ-5D-5L will be filled in on the tablet device during study visits according to the SoA or at earlier termination for those study participants discontinuing the study before completion. Completion of the EQ-5D-5L takes approximately 3 minutes.

The EQ-5D-5L is a self-administered generic and widely used measure of health status with well-documented reliability, validity and responsiveness in the general population as well as in various diseases. Use of this instrument will enable a comparison of effects of RUCC on health-related quality of life with an age-matched normative sample. The instrument comprises 5 dimensions and an overall assessment of health status on a VAS. The 5 dimensions include: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression where the scores 1 to 5 indicate: having no problems, having slight problems, having moderate problems, having severe problems and being unable to do/having extreme problems. In addition, patients are asked to self-rate their own health today on a vertical 0-100 unit VAS, with 0 corresponding to "the worst health you can imagine", and 100 corresponding to "the best health you can imagine".

Descriptive assessment will be done on the basis of the VAS and on dimension level assessment basis. The EQ-5D-5L version used in this trial is "EQ-5D-5L Tablet" © 2009 EuroQol Group EQ-5D™.

8.2 Safety Assessments

8.2.1 Physical Examinations

A comprehensive physical examination should be performed by the investigator at Visit 1 (screening), Visit 2 (Day 0) and Visit 6 (Day 84 ±2). Any abnormal findings are to be recorded and reported as an AE/SAE (see Section 8.3.1).

8.2.2 Vital Signs

Vital signs will be assessed at the site visits as specified in SoA table. This will include blood pressure (BP) and heart rate (HR) measurements. BP will be measured by using a standard sphygmomanometer with an appropriate size cuff in the sitting position after 5 minutes of rest, in a quiet setting. Blood pressure measurements can be repeated once during the screening visit if medically justified (e.g. in order to avoid suspected "white-coat hypertension".)

8.2.3 Electrocardiograms

ECGs in supine position will be assessed locally as safety measures: standard electrocardiograms (12-lead ECG) according to Goldberger / Einthoven and Wilson will be recorded after resting for at least 5 minutes at Visit 1 (screening), Visit 6 (Day 84 ±2) and SFU visit, as outlined in the SoA. The following parameters will be recorded in the eCRF: VR, PR interval, QRS duration, QT interval (corrected QT calculated according to the formulas of both Bazett and Fridericia will be automatically calculated in Rave).

(1) Fridericia´s correction: $QTc = QT/RR^{0.33}$

(2) Bazett´s correction: $QTc = QT/RR^{0.5}$

All ECG printouts will be identified with the SID as well as the date and time of recording and will be attached to participant´s file.

ECG printouts must be reviewed and evaluated locally by the investigator or clinicians with experience in ECG interpretation on the day of recording for safety and quality.

An overall investigator assessment of ECG will be provided (categories: "normal", "abnormal, not clinically significant" and "abnormal, clinically significant"). All ECG findings will be reported in the eCRF and any clinically relevant abnormality will be documented as an AE.

8.2.4 Spirometry (Lung Function Test)

Lung function testing (spirometry) will be conducted at Visit 1 (screening) in accordance with Guidelines from ATS/ERS Task Force (25), which is a standard method of the practice in pneumology. Available lung function testing results will be considered as baseline if they are not older than 3 months prior to screening.

Lung function measurements and predicted parameters calculated by the device include but are not limited to the following:

- Date
- Forced vital capacity (FVC) (L)
- Forced expiratory volume in one second (FEV1) (L)
- FEV1/FVC ratio (%)
- Forced expiratory flow (FEF) (L/sec)[6]
- Peak expiratory flow (PEF) (L/sec)
- Total lung capacity (TLC) (L)
- Vital Capacity (VC) (L)
- Inspiratory Capacity (IC) (L)
- Tidal volume (TV) (L)
- Residual volume (RV) (L)

All measured parameters that are listed above have to be transferred into the eCRF. The FEV1/FVC ratio is the ratio of the forced expiratory volume in the first one second to the forced vital capacity of the lungs. If not provided automatically by the available spirometer on site, the following formula or online tools should be applied for manual calculation (25):

FEV1/FVC ratio (FEV1%)

$$FEV1ratio = \frac{FEV1}{FVC} * 100$$

8.2.5 Clinical Safety Laboratory Assessments

The clinical laboratory tests detailed in Section 10.2 will be performed by the central laboratory.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study and after start of intervention in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator. Participants in close liver observation should be followed up as described in Section 8.3.6.

---

[6] The following FEF readouts during some fixed intervals will be recorded as part of the eCRF:
- Forced Expiratory Flow 25-75%
- Forced Expiratory Flow 50%

- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator then the results must be recorded in the eCRF in the AE page (e.g., AE or SAE)
- Details on the collection, processing, shipment and storage of samples for safety laboratory assessments will be provided in separate documents (e.g., sample handling sheets or lab manual).

The name and address for the central laboratory service provider can be found in the documentation supplied by the vendor.

Hematology and chemistry tests are to be conducted every 4 weeks. Coagulation tests will be done every 4 weeks. Prothrombin time (PT) (Quick and INR) will be determined using standard methods. Activated partial thromboplastin time (aPTT) will be measured via clotting assay.

Quantitative reverse transcription polymerase chain reaction (qRT-PCR) for SARS-CoV-2 nucleic acid detection (oropharyngeal swabs) and immunoassay for qualitative detection of IgG antibodies against SARS-CoV-2 antigen (serum) are to be performed at specified visits at the site (see Section 1.3 for details).

Since there is no established clinical relevance linked to increased ATIII activity in medical literature, it is concluded that at this stage of development, the increase in ATIII activity can be considered as not clinically relevant. In addition, given the potential for unblinding participants receiving active treatment with BAY 1817080, the results of ATIII measures at the other visits will not be communicated to study teams nor investigators until after unblinding of the study.

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g., clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

AE will be reported by the participant (or, when appropriate, healthcare professional not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study intervention.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in the SoA (Section 1.3).

A detailed history of symptoms and complications as a result of cough (type, onset, duration and time of resolution) will be recorded at screening via a series of questions reflected on an

individual eCRF page as part of the participant's medical history. Worsening of any of the conditions listed on the aforementioned eCRF page or their first occurrence after signing the informed consent will be recorded as AEs.

Additional details on smell and taste related AEs will be collected.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, female partners of male participants will be collected after the start of study intervention and until last safety follow up (SFU) visit in the study.

If a pregnancy is reported, the investigator should inform the sponsor no later than 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Liver-Related AEs

Investigators and participants should be alerted regarding non-specific symptoms which may be associated with liver dysfunction, including anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting, malaise, jaundice, fever, and rash. Information on these symptoms should be asked for in case of abnormal liver laboratory values (see Table 7–1) or any other suspicion of liver dysfunction. The study participants should be reminded to contact the study site immediately, if they are concerned about such symptoms and unscheduled liver laboratory assessments should be considered.

A 'close observation' has to be initiated in case of ALT or AST >3ULN after start of study intervention (see Table 8–1) (26).

Abnormal laboratory results and clinical signs and symptoms resulting in close liver observation (CLO) should be promptly reported as adverse event if an overarching diagnosis is not yet available.

All events of ALT >3 × upper limit of normal (ULN) and bilirubin >2 × ULN or ALT >3 × ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

Close observation includes:

- Repeat serum chemistry panel (including serum transaminases [AST and ALT] and serum bilirubin) 2 to 3 times per week. Frequency of retesting can decrease to once a week or less if laboratory abnormalities decrease and participant is asymptomatic.
- Obtaining a more detailed history of the symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis (NASH); hypoxic/ischemic hepatology and biliary tract disease. This may require performing additional procedures, e.g., ultrasound examinations. If requested, tests will be done retrospectively using residual blood/serum samples collected at visits before laboratory abnormalities occurred.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function as required, (e.g, international normalized ratio [INR], direct bilirubin measurements).

Stopping criteria for close observation:

- 2 consecutive normal/baseline results for liver enzymes in addition to availability of results from detailed CLO lab panel, related procedures, relevant medical and medication history and the reporting of signs and symptoms related to elevated liver enzymes, or
- a confirmed clinical diagnosis explaining the elevated liver enzymes.

Table 8–1: Close Observation Liver Safety Required Laboratory Assessments

Initial serum chemistry and coagulation panel	Albumin	First sample after AST or ALT > 3 X ULN
	Alkaline phosphatase	
	Alanine-aminotransferase (ALT / GPT)	
	Differential blood count	
	Cholinesterase	
	Conjugated (direct) bilirubin	
	Creatinine kinsase	
	γ-GT (gamma-GT)	
	LDH	
	Total bilirubin	
	INR, aPTT	
Hepatitis serology	Anti-Hepatitis A virus IgM antibodies	
	- Hepatitis B virus surface antigen	
	- Anti-Hep. B surface antibodies	
	- Anti-Hep. B core total antibodies	
	- Anti Hep. B IgM antibodies	
	- Hepatitis B PCR (viral copies)	
	Anti-Hepatitis C virus antibodies	
	- Hepatitis C PCR (viral copies)	
	- Anti-Hepatitis D virus antibodies (if positive, automatically test HDV RNA)	
	- Anti-Hepatitis E virus IgM (if positive, automatically test HEV RNA	
	Anti-Cytomegalovirus (CMV) IgM Antibodies	
	Anti-Epstein-Barr Virus (EBV) IgM Antibodies	
	Herpes simplex IgM (anti HSV IgM)	
Autoimmune serology	IgG level (gamma globulins)	
	Anti-mitochondrial antibodies	
	Anti-nat DNA Antibodies	
	Anti-sm Antibodies	
Metabolic and genetic etiology	A1AT level	
	Ceruloplasmin	
	Ferritin	
	Iron	
	Total iron binding capacity (TIBC)	
Follow-up samples during close observation:	Albumin	To be repeated 2 to 3 times per week until normalization of ALT or AST
	Alkaline phosphatase	
	Alanine-aminotransferase (ALT/ GPT)	

	Aspartate-aminotransferase (AST/ GOT) Blood count, full (including eosinophils) Cholinesterase CK Conjugated (direct) bilirubin Total bilirubin γ-GT (gamma-GT) Hemoglobin LDH	
Further laboratory tests to be considered*	Brucellosis, Leptospirosis (to be analysed from EDTA-blood sample), Toxoplasmosis	

*Additional further tests to be performed on case-by-case decision among Investigator, Medical Monitor and Lab Physician.

Abbreviations: A1AT = alpha-1 antitrypsin; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CK = creatine kinase; DNA = deoxyribonucleic acid; EDTA = ethylenediaminetetraacetic acid; GOT = glutamic oxaloacetic transaminase GPT = glutamic-pyruvic transaminase; GT = glutamyl transferase; HSV = Herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; PCR = polymerase chain reaction

8.4 Treatment of Overdose

- In this study, an overdose is defined as an intentional or accidental administration of investigational drug, to or by a study participant, at a dose which is higher than the dose assigned to that individual participant according to the study protocol
- There is no known specific treatment for an overdose with BAY 1817080 (no antidote)
- An overdose should be treated as clinically indicated based on signs and symptoms
- Overdose per se will not be reported as an AE and/or SAE unless it is associated with clinically relevant signs and/or symptoms, or an intentional overdose taken with possible suicidal and/or self-harming intent (see Sections 10.3.1 and 10.3.2). In these cases, if feasible, a plasma sample for PK analysis may be obtained, ideally as soon as possible after the overdose, with recording of date and time of sampling.

8.5 Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of BAY 1817080 as specified in the SoA. Samples collected at additional time points during the study will be measured too. Timing of samples collection at randomization visit (Visit 2) and EoI visit (Visit 6) is provided in Table 8–2. Timing of samples collection at week 4 (Visit 4) and week 8 (Visit 5) is provided in Table 8–3. At Visits 2 and 6, pre-dose as well as 2 hours and 4 hours post-dose samples will be collected. At Visits 4 and 5, only 6 hours post-dose samples will be collected. A ±15 min time window is allowed for all samples.

Instructions for the collection and handling of blood samples will be provided by the sponsor.

The actual date and time (24-hour clock time) of each sample, as well as the time of the last dose and the closest meal before or after that last dose will be recorded.

Samples will be used to evaluate the PK of BAY 1817080. In addition, it is planned to optionally perform an explorative metabolite analysis in human plasma. Results will be reported under separate cover, if applicable.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Details about the collection, processing, storage and shipment of samples will be provided separately (e.g., sample handling sheets or laboratory manual).

Baseline (Visit 2)

- Up to 1 hour **before** administration of the morning dose of study intervention (trough)
- 2 hours **after** administration of the morning dose of study intervention
- 4 hours **after** administration of the morning dose of study intervention

Table 8–2: PK Sampling (Visit 2)

Visit 2			Cycle of procedures			
Order of procedures	Starting point of procedures	Time interval (h)	**–1 h – 00**	**00**	**2h**	**4h**
↓	Blood sample for PK		X			
	Recording of the time and type of meal before dosing		X			
	Administration of morning dose of study intervention			X		
	Blood sample for PK				X	
	Recording of the time and the type of meal closest to the tablet intake during the visit				X	
	Blood sample for PK					X
	Recording of the time and the type of meal closest to tablet intake during the visit					X

Abbreviations: h = hours; PK = pharmacokinetic

Visits 4 and 5

- 6 hours **after** administration of the morning dose of study intervention

Table 8–3: PK Sampling (Visits 4 and 5)

Visit 4 and Visit 5			Cycle of procedures	
Order of procedures	Starting point of procedures	Time interval (h)	**00**	**6h**
↓	Administration of morning dose of study intervention		X	
	Blood sample for PK			X
	Recording of the time and the type of meal closest to tablet intake in the morning			X

Abbreviations: h = hours; PK = pharmacokinetic

End of Intervention (Visit 6)

- Up to 1 hour **before** administration of the morning dose of study intervention (trough)
- 2 hours **after** administration of the morning dose of study intervention
- 4 hours **after** administration of the morning dose of study intervention

Table 8–4: PK Sampling (Visit 6)

Visit 6			Cycle of procedures			
Order of procedures	Starting point of procedures	Time interval (h)	**–1 h – 00**	**00**	**2h**	**4h**
↓	Blood sample for PK		X			
	Recording of the time and the type of meal closest to the tablet intake in the evening before the visit		X			
	Administration of morning dose of study intervention			X		
	Blood sample for PK				X	
	Recording of the time and the type of meal closest to the tablet intake during the visit				X	
	Blood sample for PK					X
	Recording of the time and the type of meal closest to the tablet intake during the visit					X

Abbreviations: h = hours; PK = pharmacokinetic

Population pharmacokinetic (popPK) analysis

The systemic exposure of BAY 1817080, drug-related pharmacodynamic (PD) biomarker and/or safety and efficacy measurements collected during the trial might be analyzed using nonlinear mixed effects modeling.

Mixed effects models, e.g., popPK models, describe the relationship between dose and time and variables such as drug plasma concentrations. Both structural and random effects are involved in this relationship. A preliminary popPK compartmental model will be further developed using the concentration of the drug as the dependent variable.

The potential influence of relevant participant covariates (e.g., body weight) and optionally efficacy, PD biomarkers or safety laboratory parameter can be included in the PK/PD modeling using population approaches. A separate evaluation plan, providing details of the model building process and evaluation will be provided prior to the beginning of the popPK/PD analysis. Results obtained by popPK/PD modeling will be presented in a separate report that may also include PK data from other studies with BAY 1817080.

The modeling analyses might be started prior to database lock. If this is applicable, appropriate measures will be taken to maintain blinding of the study team, e.g., data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

Plasma concentration data for all participants will be listed in the clinical study report.

8.6 Pharmacodynamics

See Section 8.5 for details.

8.7 Genetics

Genetic as well as non-genetic analyses will be part of the biomarker investigations in this study. See Section 8.8 for details.

8.8 Biomarkers

In this study, genetic as well as non-genetic biomarkers will be investigated. Genetic investigations may be of any kind, except for whole genome sequencing.

Blood samples will be collected for biomarkers as indicated in the SoA.

- **Timing:** see Section 1.3 for planned time-points of sample collection.
- **Sample handling and storage:** details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g., sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.
- **Reporting:** the results of biomarker investigations may be reported separately (e.g., in the Biomarker Evaluation Report).

8.8.1 Biomarkers Monitoring Disease Activity

Various factors may be involved in the pathogenesis of the syndrome of RUCC. To further investigate potential mechanisms affected by BAY 1817080, candidate biomarkers indicative of disease activity will be investigated in blood samples. Candidate monitoring biomarkers may include (but are not limited to), for example neurogenic and/or inflammatory markers.

8.8.2 Pharmacogenetic Biomarkers

Genetic predisposition that might be associated with treatment response to BAY 1817080 and/or genetic determinants of cough sensitivity and/or associated comorbidities will be investigated.

The phenotypic heterogeneity of patients may be caused by genetic factors (27). In needs to be explored, whether some of the recently discussed genetic variants within neuropathic processing contribute to cough sensitivity and response to therapy in chronic pain. DNA samples will be utilized for genotyping of candidate genes suggested to play a role in cough syndrome, neuropathic processes and/or afferent hypersensitivity.

A blood sample will be obtained from those participants, who have signed an informed consent form. The sample may be used as source of germline DNA.

Pharmacogenetic analyses may include targeted sequencing of the candidate genes and allele specific PCR analyses, for example. The methods will be chosen according to current state of the art.

Details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g., sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.

The results of genetic investigations may be reported separately (e.g., in the Biomarker Evaluation Report).

8.8.3 Other Biomarkers

In addition to the biomarkers described in Sections 8.8.1 and 8.8.2, further biomarkers related to the mode of action or the safety of BAY 1817080 and similar drugs may be examined. The same applies to further biomarkers deemed relevant to pulmonary diseases and associated health problems. These investigations may include e.g., diagnostic, safety, PD, monitoring, or potentially predictive biomarkers.

8.9 Health Economics / Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1 Statistical Hypotheses

The primary endpoint for this study will be the change from baseline in 24-hour cough count after 12 weeks of intervention. The primary efficacy aim is the detection of a trend in the dose relationship for the primary efficacy endpoint. For detecting an overall trend, or a dose-response signal, each of the dose-response shapes in the candidate set will be tested, i.e., the null hypotheses: "The response at all doses is equal" will be tested against the alternative "There is a dose-response-relationship". This will be done using a single contrast test based on contrast coefficients, taking the actual estimated effect per intervention group into account.

For each of the $K = 4$ intervention groups (i.e., the placebo group and the 3 active intervention groups of BAY 1817080) the response is $\mu_k, k = 1, \dots, K$.

For each model m, $m = 1, \dots, 4$, in the candidate set

the null hypothesis $H_{0m}: c_m\ \mu_m = 0$

will be tested against

the respective 1-sided alternative hypothesis $H_{1m}: c_m\ \mu_m\ > 0,$

where $c_m = (c_{m1}, \dots, c_{mk})'$ is an optimized contrast vector for the doses,
$\mu_m = (\mu_{m1}, \dots, \mu_{mk})' = (f_m(d_1, \theta_m), \dots, f_m(d_K, \theta_m))'$ and
f is the dose-response model $\mu_m = f(d, \theta) + \epsilon$.

A more detailed description of the multiple comparison procedure modelling (MCP-Mod) approach and the models used will be given in Section 9.4.

9.2 Sample Size Determination

Sample size calculations were performed for establishing evidence of a drug effect across the doses, that is, detecting a statistically significant dose response signal for the primary efficacy outcome in this study using the MCP-Mod approach.

Treatment effects are here presented on the log scale of average hourly counts, measured over 24 hours (see Section 9.4.2 for calculation details and interpretation).

Assuming a true change in cough count under placebo after 12 weeks of -0.19 (17% reduction), a maximum cough count change of -0.35 for BAY 1817080 over placebo (30%

reduction relative to placebo), a common standard deviation of 0.8, a set of plausible dose-response shapes including Emax and sigmoidal Emax models (chosen based on BAY 1817080 effects in Study 18184 combined with literature review), random allocation of participants to dose groups according to a 1:1:1:1 ratio, a sample size of 50 participants per dose groups will have at least 85% power to demonstrate a dose- response relationship, using a one-sided test at a type I error rate of α=0.10. Approximately 236 participants will be randomized to achieve 200 evaluable participants for an estimated total of 50 evaluable participants per intervention group. The number of participants to be randomized might be increased if more participants than expected become unevaluable due to COVID-19 related circumstances, to maintain the goal of 50 evaluable participants per intervention group.

With this sample size, the dose-response curve is expected to be estimated with 80% confidence bands of half-widths of 0.14 to 0.16, depending on the underlying dose-response relationship.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Full analysis set (FAS)	All participants randomly assigned to study intervention.
Safety analysis set (SAF)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Per protocol set (PPS)	All participants randomly assigned to study intervention, who have no validity findings affecting efficacy. Further details will be specified in the SAP, ACIR and the BRR.

Abbreviations: ACIR = Assessment Criteria and Identification Requirement; BRR = Blind Review Report; ICF = informed consent form; SAP = statistical analysis plan

The efficacy endpoints will be analyzed using the PPS, with analyses on the FAS serving as sensitivity analyses. The safety endpoints will be analyzed using the SAF.

9.4 Statistical Analyses

9.4.1 General considerations

The statistical analysis plan (SAP) will be developed and finalized before unblinding of the database and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. It will provide further details on the planned analysis for all efficacy, safety and other endpoints.

This section is a summary of the planned statistical analyses with focus on the primary and secondary efficacy endpoints.

The statistical analyses will be performed using SAS; the version used will be specified in the SAP. There will be separate analysis plan for psychometric properties, scoring and assessment of SCCD.

Continuous variables will be analyzed using at least the following descriptive statistics: number of non-missing observations, arithmetic mean and standard deviation, median, minimum and maximum. Discrete data will be analyzed using frequency tables.

The primary efficacy analysis is based on a while on treatment estimand strategy. The goal is to estimate the effect of the intervention in those participants who tolerate the intervention, adhere to the intervention schedule and follow all relevant protocol procedures. The analysis will be performed on the PPS population. The primary variable will be the change from baseline in 24-hour cough count after 12 weeks of intervention. The intercurrent events "discontinuation of study intervention" and "non-compliance with study intervention" will be handled with the while on treatment strategy, and for participants experiencing such an event, the last observation of the endpoint prior to the event will be carried forward. Participants with intercurrent events that lead to exclusion from the PPS will be excluded from the analysis. Handling of intercurrent events related to COVID-19 will be described in the SAP. Other intercurrent events will be disregarded. The population-level summary will be the estimated mean of change from baseline in the logarithm of average hourly cough count by intervention group.

9.4.2 Primary Endpoints

The primary efficacy endpoint is the change from baseline in 24h cough count after 12 weeks of intervention. Baseline is defined as the measurement at Visit 2. The raw 24h cough count will be standardized to an average hourly count, and then log-transformed for the analysis due to the expected range and distribution of the data. After applying a log-transformation, the data are expected to be normally distributed.

The primary analysis will be performed on participants in the PPS who have valid cough count measurements both at baseline and at least one post-baseline measurement. Supporting analyses will be performed on the FAS. Further sensitivity analyses will be specified in the SAP.

The MCP-Mod method combining MCP (multiple comparison procedures) principles with modeling techniques will be used for the primary statistical analysis. This method allows the flexibility of modeling for dose estimation, while preserving the robustness to model misspecification associated with MCP procedures.

3 active doses of BAY 1817080 will be used in this study: 25 mg, 75 mg, and 150 mg BID, with an additional placebo arm, corresponding to a 0 mg dose. The measurement of the primary efficacy endpoint at dose x will be a normally distributed variable μ_x, i.e., the change from baseline in log (average hourly cough count). For the dose-response relationship we assume

$$\mu_x = f(x, \theta) + \epsilon.$$

It is assumed that the change from baseline after 12 weeks of intervention is -0.19 under placebo and -0.54 at the maximum possible dose.

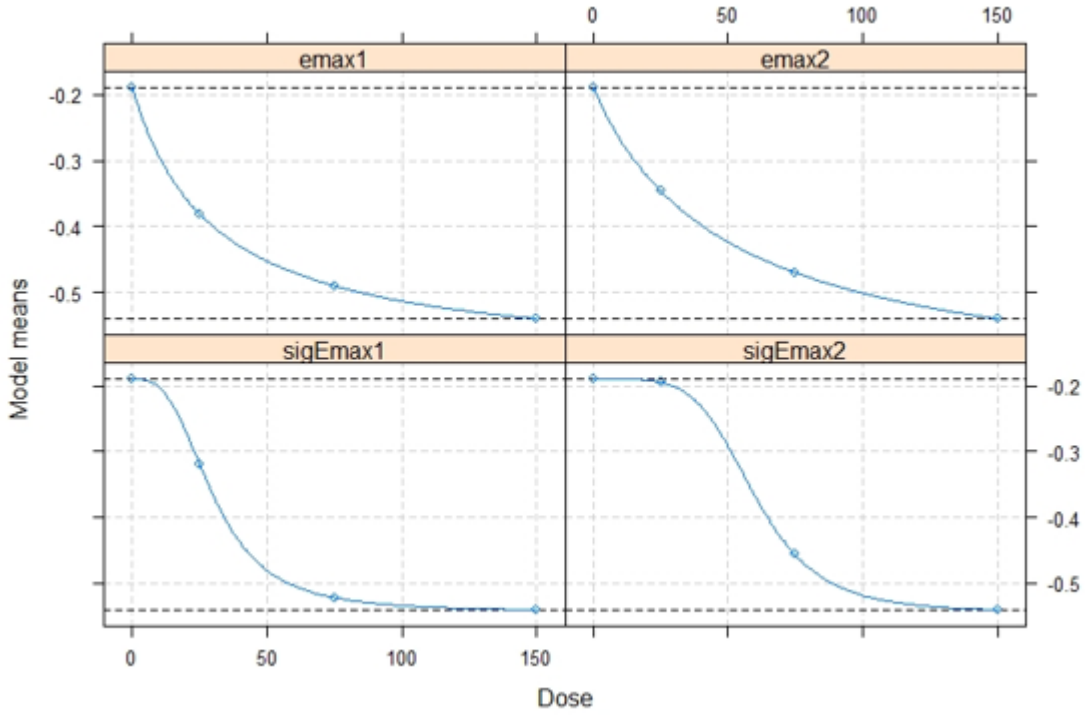
The candidate set of models for $f(x, \theta)$ consists of four models, two Emax models with parameter ED_{50}= 30 and ED_{50}= 50 and two sigmoidal models with the parameters $ED_{50} = 30$ and $Hill = 3$, and $ED_{50} = 60$ and $Hill = 5$. All these candidate models assume a monotonically decreasing dose-response. The parameters of the models are based on Phase 2a data and literature review. The dose-response candidate models are shown in Table 9–1.

Table 9–1: Dose-Response Candidate Models

Model	Response as function of dose d
Emax1	*-0.19 - 0.42 * d / (30 + d)*
Emax2	*-0.19 - 0.47 * d / (50 + d)*
sigmoidal Emax1	*-0.19 - 0.35 * d^3/(30^3 + d^3)*
sigmoidal Emax2	*-0.19 - 0.35 * d^5/(60^5 + d^5)*

The corresponding dose-response relationships of the candidate models are shown in Figure 9–1.

Figure 9–1: Candidate Set of Dose Response Curves



Based on these models and the observed data optimal contrasts c_m and the corresponding critical value will be calculated. A more detailed description will be provided in the SAP.

Based on the optimal contrast and the critical values a one-sided test with $\alpha = 0.1$ based on the maximum value of the test statistics for the models in the candidate set will be performed. The MCP-Mod method takes multiplicity into account, and thus no further multiplicity adjustments have to be performed.

If at least one contrast test is statistically significant, then a dose-response signal is considered to be established. The best model can be selected out of the statistically significant models in the candidate set for the next step: modeling and estimation. The selection of the dose-estimation model will be based on an assessment of the p value. If no candidate model is statistically significant, the procedure stops indicating that a dose-response relationship cannot be established from the observed data.

Supportive and sensitivity analyses will include pairwise comparisons of each active dose with placebo, and corresponding analyses on the FAS. Further details will be given in the SAP.

9.4.3 Secondary Endpoints

The following table gives an overview of the secondary efficacy endpoints and outlines the key features of the planned analyses. Further details will be provided in the SAP.

Secondary Efficacy Based on Cough Counts • Percentage of participants with a ≥30% reduction from baseline in 24-hour cough count after 12 weeks of intervention (measured by cough recording digital wearable monitoring device) • Change from baseline in 24-hour cough count after 2, 4, and 8 weeks of intervention (measured by cough recording digital wearable monitoring device) • Change from baseline in awake cough frequency per hour after 2, 4, 8 and 12 weeks of intervention (measured by cough recording digital wearable monitoring device)	• The proportion of participants meeting the responder threshold will be compared across intervention groups using a Chi-square test. • The secondary efficacy endpoints of cough count at different time points and awake cough count will be analyzed similar to the primary efficacy endpoints
HrQoL and PRO Associated Secondary Endpoints • Change from baseline in cough related quality of life (measured by Leicester Cough Questionnaire) after 12 weeks of intervention • Change from baseline in cough severity after 12 weeks of intervention (measured by Cough Severity Visual Analogue Scale (VAS)) • Percentage of participants with a ≥30 scale units reduction from baseline after 12 weeks of intervention (measured by cough Severity VAS) • Percentage of participants with a ≥1.3-point increase from baseline after 12 weeks of intervention (measured with Leicester Cough Questionnaire (LCQ) Total Score)	• The change from baseline will be analyzed by means of a mixed-model for repeated measurements (MMRM). This will be further detailed in the SAP • The proportion of participants meeting VAS and LCQ responder thresholds by intervention group will be compared across intervention groups using a Chi-square test.

The secondary endpoint of TEAEs will be analyzed by descriptive statistics, such as frequency tables. All TEAEs will be tabulated according to the affected system organ class and preferred term, as coded by the Medical Dictionary for Regulatory Affairs (MedDRA). Further tables will be provided for serious and/or drug related TEAEs.

A TEAE is defined as any event arising or worsening after the start of study drug administration until 14 days after the last study medication intake.

The summaries will be provided by intervention group and overall.

9.4.4 Exploratory Endpoints

The analysis of the exploratory endpoints will be described in the SAP.

9.4.5 Other Safety Endpoints

All safety analyses will be performed on the Safety Analysis set (SAF). All tabulations will be descriptive.

The number of participants with pre-treatment and post-treatment AEs will be also assessed.

9.4.6 Other Analyses

Summary statistics will be presented by intervention group and overall. Frequency tables for qualitative data will be provided. Medical history findings will be summarized using MedDRA terms.

PK, PD, and biomarker exploratory analyses will be described in the SAP finalized before database lock, or in separate analysis plans. The population PK/PD analysis will be presented separately from the main clinical study report (CSR).

The psychometric properties of SCCD will be evaluated to support qualification of SCCD as an endpoint for RUCC. These exploratory analyses results will be presented separately from the CSR.

In addition, the dose-dependency of taste-related AEs will be assessed using a logistic regression model.

Any other pre-specified analyses will be described in the SAP finalized before database lock.

9.5 Interim Analyses

Not applicable to this study.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator may be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests prior to the start of study, and in case of any changes, within 1 year after completion of the study.

10.1.3 Informed Consent Process

The investigator will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC and study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

10.1.4 Data Protection

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

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

A Steering Committee will be established to ensure a proper study conduct according to the state of the art. The Steering Committee will be responsible for all scientific aspects of the

study and it will ensure that study execution and management of the study are of the highest quality. The Steering committee will consist of investigators and a chair.

10.1.6 Dissemination of Clinical Study Data

Result Summaries of Bayer's sponsored clinical trials in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers' patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) on or after 01 JAN 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (e.g., cough recorder data, PRO date, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for at least 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be

destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Cough recordings and records entered on the tablet and hand-held device are considered source data. All other source data will be specified on the Source Data Identification Check List.

10.1.9 Study and Site Start and Closure

The study start date is the date of first patient first visit (FPFV).

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

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate subject therapy and/or follow-up

10.1.10 Publication Policy

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

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site 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.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10–1 will be performed by the central laboratory, apart from urine pregnancy tests which are to be done at the trial sites.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Table 10–1: Protocol-Required Safety Laboratory Assessments

Laboratory assessments	Parameters
Hematology	Erythrocytes, Hemoglobin, Hematocrit, Leukocytes, Platelets
Blood Chemistry[1]	Sodium, Potassium, Calcium, Magnesium, Phosphorus, Creatinine, Cystatin C, Total protein, Albumin, eGFR [2]
Liver enzymes	Alkaline phosphatase, γ-GT (gamma GT), Alanine-aminotransferase (ALT, former GPT), Aspartate-aminotransferase (AST, former GOT), Total bilirubin
Carbohydrate metabolism	Serum glucose, Hemoglobin-A1C (HbA1C)
Lipids	Total cholesterol, Triglyceride, HDL-cholesterol, LDL-cholesterol
Coagulation	Prothrombin time (Quick), Activated partial thromboplastin time (aPTT), Fibrinogen, International normalized ratio (INR), Antithrombin III (ATIII) [3]
Pancreas	Pancreatic α-amylase, Lipase
Pregnancy testing[4]	For women of child-bearing potential only, serum test at Visit 1, otherwise urine pregnancy tests every 4 weeks until the last study visit (SFU Visit)
COVID-19 testing[5]	Quantitative reverse transcription polymerase chain reaction (qRT-PCR) for SARS-CoV-2 nucleic acid, SARS-CoV-2 Immunoglobulin G antibodies

NOTES:

1 Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.3.6. All events of ALT >3 × upper limit of normal (ULN) and bilirubin >2 × ULN or ALT >3 × ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE .

2 Estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease (MDRD) formula. Japan-specific formula will be applied for participants enrolled at Japan sites (see Section 10.6).

3 Screening ATIII results will be available to the investigator/sites as soon as measured and reported by the central laboratory. Considering the potential for unblinding participants receiving active treatment with BAY 1817080, the results of ATIII measures at the following visits will not be communicated to study teams nor investigators until after unblinding of the study.

4 All study-required laboratory assessments will be performed by a central laboratory, with the exception of urine pregnancy tests.

5 An oropharyngeal swab will be collected for quantitative measurement of the virus and serum will be collected for measurement of antibodies (serology).

Abbreviations: ALT = alanine aminotransaminase; ATIII = antithrombin III; GOT = glutamic oxaloacetic transaminase; GPT = glutamic-pyruvic transaminase; GT = glutamyl transferase; HDL = high-density lipoprotein; INR = International normalized ratio; MDRD = Modification of Diet in Renal Disease; SAE = serious adverse event; SFU = safety follow-up; ULN = upper limit of normal

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

Time period and frequency for collecting AEs and SAEs can be found in Section 8.3.1.

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention (for definition of study intervention, see Section 6).

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**

a. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

b. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

c. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

d. Is a congenital anomaly/birth defect

e. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
  - Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor with a copy of any post mortem findings (autopsy report).
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Contacts for SAE reporting can be found in the Investigator Site File.

SAE Reporting to the Sponsor via Paper CRF

- Electronic data transmission of the SAE is the preferred method to transmit this information to the sponsor's Pharmacovigilance department
- In rare circumstances and in the absence of email, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRFs within the designated reporting time frames
- Paper SAE forms (CRFs), details and contacts for SAE reporting can be found in the Investigator Site File

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use acceptable effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

(See also the Inclusion Criteria in Section 5.1.)

Acceptable effective birth control methods which may not be considered as highly effective (as per CTFG guidelines):

Acceptable effective birth control methods that result in a failure rate of more than 1% per year include:

- progestogene-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

- male or female condom with or without spermicide[7]
- cap, diaphragm or sponge with spermicide[7]

Highly effective birth control methods (that can achieve a failure rate of less than 1% per year when used consistently and correctly) include (as per CTFG guidelines):

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner[8]
- Sexual abstinence[9]

No measures are required for male participants

Collection of Pregnancy Information:

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who have received at least one dose of study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor as being aware of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor.

---

[7] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[8] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[9] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study interventions. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who Become Pregnant

- The investigator will collect pregnancy information on any female participant whose pregnancy is detected after the first dose of study intervention. The initial information will be recorded on the appropriate form and submitted to the sponsor within of 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, after obtaining the signed informed consent from both parents, unless local law or specific circumstances of the respective case allow otherwise, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any female participant who becomes pregnant while participating in the study must discontinue study intervention.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5 Appendix 5: Device Malfunction or Failure and Medical Device Related Events Reporting

A Product Technical Compliant (PTC) is any report about a potential or alleged failure of a product in its quality (including the identity, durability, reliability, safety, efficacy or performance) or suspect counterfeit. The complaint may or may not represent a potential risk to the participant.

Any malfunction or failure of the cough recording device (VitaloJAK™) including use errors or inadequacy in the labeling will be recorded by the clinical/investigational site, including all relevant device information, and reported directly to the manufacturer.

There are three different situations, in which a PTC might need to be reported by the investigator.

a. When an AE is recorded, the investigator needs to check if a device assigned and worn by the corresponding participant operates as intended.
b. When a device malfunction or device failure occurs, the investigator needs to assess whether an AE might have occurred in relation to the device complaint.
c. When a device malfunction, device failure, or use error occurs, without any associated AE, this also needs to be captured in the form, especially if it classifies as a reportable incident, and immediately forwarded to the sponsor for PTC investigation.

There are three different categories of medical device related events

Incident

Any malfunction or deterioration in the characteristics and / or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, led, might lead to or might have led to the death of a participant, or user or of other persons or to a serious deterioration in their state of health.

Other reportable incident

Any incident that did not lead to death or serious deterioration in health, but it might do if it occurred again under less fortunate circumstances or without intervention of healthcare personnel. This may include cases without any medical event reported.

Non-incident

Any device related case that does not fulfill all the three basic incident criteria a-c listed in the definition of an “incident” above. This includes reports of:

- Deficiencies of a device which are always detected prior to its use
- Event is caused by the participant’s condition
- Service life or shelf life of the device is expired
- Events which did not lead to serious deterioration in state of health or death, because a design feature protected against a fault becoming a hazard.
- Events where the risk of a death or serious deterioration in state of health has been quantified and found to be negligibly small.

In case of an incident and other reportable incident, a PTC always needs to be reported.

Serious deterioration in state of health (=serious injury) is any AE in relation to a medical device if it:

- Resulted in a life-threating illness or injury, or
- Resulted in a permanent impairment of a body structure or a body function, or
- Required in-patient hospitalization or prolongation of existing hospitalization, or
- Resulted in medical or surgical intervention to prevent life-threating illness, or permanent impairment of a body function or damage to a body structure, or
- Led to fetal distress, fetal death or congenital abnormality or birth defect.

The details of the malfunction and medical circumstances will be captured by the investigator and then returned to the sponsor.

The processing and reporting of all reportable device events (incidents /other reportable incidents) to the authorities will be done by the manufacturer of the device.

10.6 Appendix 6: Country-specific Requirements

The estimation of GFR is limited by differences in creatinine generation among ethnicities. Thus, the MDRD GFR equation is less accurate for Asians, with greater bias at eGFR less than 30 mL/min/1.73 m^2. In Japan, the equation recommended by the Japanese Society of Nephrology (28) will be used for participants enrolled at Japan site in this study.

- For men: $eGFRcreat(mL/min/1.73m^2) = 194 \times Cr^{-1.094} \times age^{-0.287}$
- For women: $eGFRcreat(mL/min/1.73m^2) = 194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739$

10.7 Appendix 7: Abbreviations

AE	Adverse event
AG	Aktiengesellschaft, public limited company
ALT	Alanine aminotransaminase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransaminase
ATIII	Antithrombin III
ATP	Adenosine triphosphate
ATS	American Thoracic Society
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BID	Bis in die (twice daily)
BP	Blood pressure
CFR	Code of Federal Regulations Title 21
CI	Cognitive interview
CLO	Close liver observation
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTFG	Clinical Trials Facilitation and Coordination Group
Ctrough	Trough concentration
CYP3A4	Cytochrome P450 3A4
DBP	Diastolic blood pressure
DDI	Drug Development and Drug Interactions
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
eGFRcreat	eGFR using the serum creatinine
EoI	End of intervention
ePRO	Electronic patient report outcome
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Scale
ERS	European Respiratory Society
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full analysis set

FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV	Forced expiratory volume
FEV1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good clinical practice
GFR	Glomerular filtration rate
GLP	Good laboratory practice
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
GT	Glutamyl transferase
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HR	Heart rate
HrQoL	Health-related quality of life
HRT	Hormonal replacement therapy
HSV	Herpes simplex virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobin G
IgM	Immunoglobin M
IND	Investigational new drug
INR	International normalized ratio
IRB	Independent Review Board
IWRS	Interactive Web Response System
kHz	Kilohertz
LCQ	Leicester Cough Questionnaire
LDH	Lactate dehydrogenase
MCP	Multiple comparison procedure
MCP-Mod	Multiple comparison procedure modelling
MD	Medical doctor
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
OATP1B1	Organic anion transporting polypeptide 1B1

OATP1B3	Organic anion transporting polypeptide 1B3
P2X3	Purinergic receptor P2X
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
P-gp	P-glycoprotein
PIF	Photoirritation factor
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetic(s)
PPS	Per protocol set
PRO	Patient reported outcome
PT	Prothrombin time
PTC	Product Technical Complaint
QoL	Quality-of-life
qRT-PCR	Quantitative reverse transcription polymerase chain reaction
RNA	Ribose Nucleic Acid
RO	Receptor occupancy
RUCC	Refractory and/or unexplained chronic cough
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis System
SCCD	Severity of Chronic Cough Diary
SFU	Safety follow-up
SoA	Schedule of Activities
SOP	Standard operating procedure
SUKL	State Institute for Drug Control (Czechia Health Authority)
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
TLC	Total lung capacity
TV	Termination visit
ULN	Upper limit of normal
UV	Ultraviolet
VAS	Visual Analogue Scale
VR	Ventricular rate
WAV	Waveform audio file format

WOCBP	Woman of childbearing potential

10.8 Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.8.1 Amendment 1 (17 JUL 2020)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The main purpose of this global amendment is to address COVID-19 pandemic related issues. Changes include additional benefit risk assessments, exclusion criteria as well as COVID-19 testing for participants. The discontinuation criteria was also modified to explain how to manage participants who get infected with COVID-19 while on study.

Other changes have also been made in this global amendment. Following are the description of change and a brief rationale.

These changes do not affect the design or the overall concept of the study.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA), 8.2.5 Clinical Safety Laboratory Assessments and 10.2 Appendix 2: Clinical Laboratory Tests	COVID-19 testing was added. Survival status check was added for participants who do not show up at the safety follow-up visit.	To address issues related to the COVID-19 pandemic.
2.3 Benefit/Risk Assessment	A new Section 2.3.3.7 Risk of contracting SARS-CoV-2 infection during study participation was added.	
5.2 Exclusion Criteria	COVID-19 related exclusion criteria #18 was added.	
7.1.1 Rechallenge	Criteria for rechallenge was added.	
7.2 Participant Discontinuation/Withdrawal from the Study	Withdrawal from study criteria added to clarify what to do if a participant becomes SARS-CoV-2 virus RNA positive while on study.	
9.2 Sample Size Determination and 9.4.1 General considerations	Statistical considerations adjusted for COVID-19 related issues.	
1.3 SoA, 5.2 Exclusion Criteria, and 8.2.2 Vital Signs	Exclusion criteria #11 was modified to exclude participants with systolic/diastolic blood pressure levels ≥160/100 mmHg at the screening visit.	To align with the local amendment for Czechia (to satisfy the request from Czechia Health Authority, State Institute for Drug Control [SUKL]).

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 3 Objectives and Endpoints and 9.4.3 Secondary Endpoints 9.4.5 Other Safety Endpoints	The secondary endpoint for safety and tolerability evaluation was changed to "frequency and associated severity of treatment-emergent adverse events (TEAEs)". The incidence of AEs during pre-treatment and post-treatment periods was added as other safety endpoints.	To align with other studies within P2X3 program.
1.3 SoA and 6.1 Study Intervention Administered	V6/TV was changed to be a 2-day visit.	To clarify when cough recording device will be dispensed and when other procedures could be conducted at V6/TV.
2.3.1 Summary	The introduction of chronic cough was edited.	To address comment from the Steering Committee.
2.3.3.6 Potential Phototoxicity	PIF value was corrected.	Correction of error.
4.1 Overall Design and 5.1 Inclusion Criteria	Inclusion criteria #2 was modified for clarification.	To address potential misinterpretations.
6 Study Intervention	The definition of study intervention was added.	For clarification.
6.5 Prior and Concomitant Therapy	Text for Section 6.5.1 Other Treatment Considerations was adjusted.	To align with the request from FDA.
	Text "up to 12 weeks prior to screening" was added to the definition of prior and concomitant therapy. In Table 6-2: the prohibited timeframe of apixaban, dabigatran, edoxaban, digoxin was edited to reflect "until 2 weeks after end of intervention (EoI)"; over-the-counter cough medicine was adjusted to include all non-narcotic cough medicine.	For clarification.
	In Table 6-2: phenobarbital was removed from the strong CYP3A4 inducers examples.	Correction of error.
8. Study Assessments and Procedures	Text on cough history recording was copied and added from Section 8.3.1.	For clarification.
8.2.1 Physical Examinations and 1.3 SoA	"Day 1" of Visit 2 was changed to "Day 0" to match the SoA.	Correction of error.
8.3.1 Time Period and Frequency for Collecting AE and SAE information	Added that additional details on smell and taste related AEs will be collected.	This was erroneously missed in the original protocol.
8.3.1 Time Period and Frequency for Collecting AE and SAE information,	The collection of AEs was changed to "commence from signing the informed consent	To align with other studies within P2X3 program.

Section # and Name	Description of Change	Brief Rationale
1.3 SoA, 8.2.1 Physical Examinations, and 8.2.3 Electrocardiograms	form".	
8.3.6 Liver-Related AEs	Stopping criteria for close observation was added. Hepatitis serology tests for hepatitis D and E was added in Table 8-1.	This was erroneously missed in the original protocol.
	Hepatitis B core IgG antibody test was removed from Table 8-1.	Correction of error.
8.3.6 Liver-Related AEs, 2.3.3.4 Potential Changes in Liver Function Laboratory Parameters, 7.1 Discontinuation of Study Intervention, and 10.2 Appendix 2: Clinical Laboratory Tests	The criteria for liver-related AE and SAE reporting was modified.	To address the inconsistency throughout the document.
8.5 Pharmacokinetics	Text for explorative metabolite analysis was added.	To align with the request from FDA.
9.4.6 Other Analyses	Text for dose-dependency of taste-related AEs was moved from Section 9.4.3 to 9.4.6.	This was erroneously put under the analysis of the secondary endpoints in the original protocol.
10.2 Appendix 2: Clinical Laboratory Tests	"Japan-specific MDRD formula" corrected to be "Japan-specific formula" in Table 10-1 footnote #2.	Correction of error.

In addition, minor editorial and formatting revisions have been made throughout the document.

10.9 References

1. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis. 1990;141(3):640-7.
2. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet. 2008;371(9621):1364-74.
3. Morice AH, Jakes AD, Faruqi S, Birring SS, McGarvey L, Canning B, et al. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. Eur Respir J. 2014;44(5):1149-55.
4. French CL, Irwin RS, Curley FJ, Krikorian CJ. Impact of chronic cough on quality of life. Arch Intern Med. 1998;158(15):1657-61.
5. Belvisi MG, Birrell MA, Wortley MA, Maher SA, Satia I, Badri H, 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(10):1255-63.
6. Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):1s-23s.
7. Achilleos A. Evidence-based Evaluation and Management of Chronic Cough. Med Clin North Am. 2016;100(5):1033-45.
8. Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Ribas CD, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J. 2019:1901136.
9. NCT03310645. Repeat Doses of BAY 1817080 in Healthy Males & Proof of Concept in Chronic Cough Patients. Bayer. 2017. ClinicalTrials.gov.
10. Song WJ, Chang YS, Faruqi S, Kim JY, Kang MG, Kim S, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. Eur Respir J. 2015;45(5):1479-81.
11. Morice AH, Kitt MM, Ford AP, Tershakovec AM, Wu WC, Brindle K, et al. The effect of gefapixant, a P2X3 antagonist, on cough reflex sensitivity: a randomised placebo-controlled study. Eur Respir J. 2019;54(1).
12. NCT02612610. A 12-Week Study to Assess the Efficacy and Safety of AF 219 in Subjects With Refractory Chronic Cough (MK-7264-012). Afferent Pharmaceuticals, Inc. 2015. ClinicalTrials.gov.
13. Schumann J, Boudon S, Ulrich P, Loll N, Garcia D, Schaffner R, et al. Integrated preclinical photosafety testing strategy for systemically applied pharmaceuticals. Toxicol Sci. 2014;139(1):245-56.
14. Brignall K, Jayaraman B, Birring SS. Quality of life and psychosocial aspects of cough. Lung. 2008;186 Suppl 1:S55-8.
15. Turner RD, Bothamley GH. Cough hypersensitivity syndrome: clinical measurement is the key to progress. Eur Respir J. 2015;45(5):1507-8.
16. Morice AH, Fontana GA, Belvisi MG, Birring SS, Chung KF, Dicpinigaitis PV, et al. ERS guidelines on the assessment of cough. Eur Respir J. 2007;29(6):1256-76.
17. Davidson K, Shojaee S. Managing Massive Hemoptysis. Chest. 2019:S0012-3692(19)31386-8.
18. FDA. FDA Guidance for Industry: In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Available on:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions. Accessed date: 03 Jul 2020. 2020.

19. FDA. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers,Table 5-1. 14Nov2017.Available online: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-1 Accessed date: 05Nov2019. 2017.
20. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health. 1990;13(4):227-36.
21. Lee KK, Matos S, Evans DH, White P, Pavord ID, Birring SS. A longitudinal assessment of acute cough. Am J Respir Crit Care Med. 2013;187(9):991-7.
22. NCT03449147. A Study of Gefapixant (MK-7264) in Adult Participants With Chronic Cough (MK-7264-030). Merck Sharp & Dohme Corp. 2018. ClinicalTrials.gov.
23. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58(4):339-43.
24. Raj AA, Pavord DI, Birring SS. Clinical cough IV:what is the minimal important difference for the Leicester Cough Questionnaire? Handb Exp Pharmacol. 2009(187):311-20.
25. Philip H. Quanjer SS, Tim J. Cole, Janet Stocks. GLI-2012 Desktop Software for Individual Calculations. Global Lung Function Initiative. Available from: https://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/desktop-individual-calculator.aspx. Dec. 2014.
26. FDA Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Available online: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation. Accessed date 11Nov2019. 2009.
27. Mazzone SB, Chung KF, McGarvey L. The heterogeneity of chronic cough: a case for endotypes of cough hypersensitivity. Lancet Respir Med. 2018;6(8):636-46.
28. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised Equations for Estimated GFR From Serum Creatinine in Japan. American Journal of Kidney Diseases. 2009;53(6):982-92.