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.

1.3 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

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

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

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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).

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.

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

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™.

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.

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[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.

	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.

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

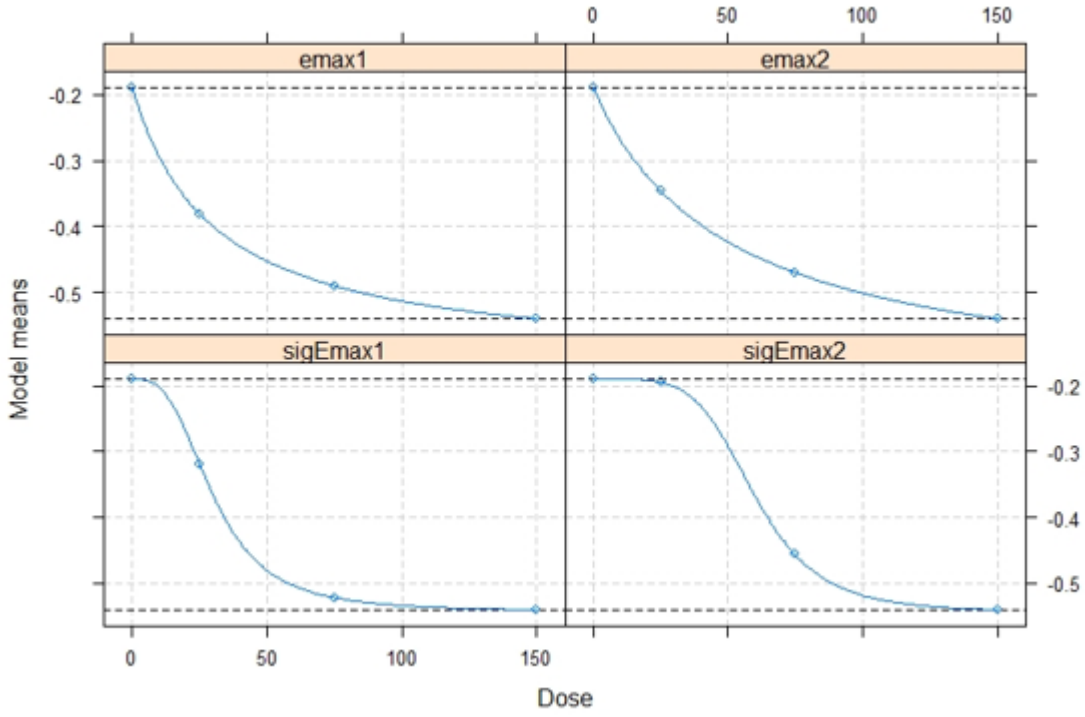
See Section 8.5 for details.

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.

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

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

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

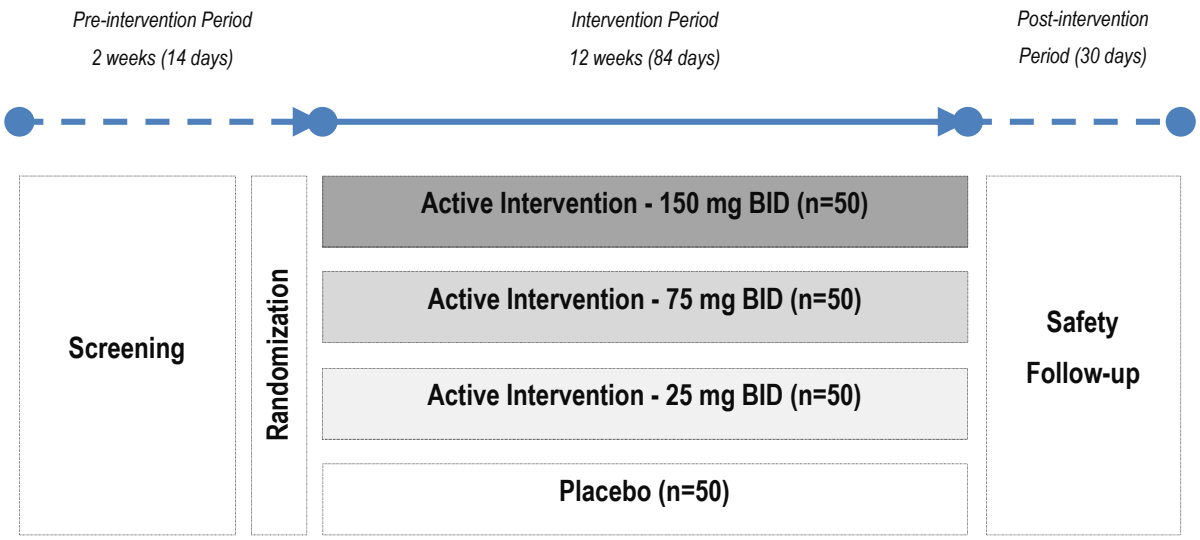
The estimation of GFR is limited by differences in creatinine generation among ethnicities. Thus, the MDRD GFR equation is less accurate for Asians, with greater bias at eGFR less than 30 mL/min/1.73 m^2. In Japan, the equation recommended by the Japanese Society of Nephrology (28) will be used for participants 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: $eGFRcreat(mL/min/1.73m^2) = 194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739$

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

1.2 Schema

Figure 1–1: Study design



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

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.

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.

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).

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.

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

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.

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).

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

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).

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.

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

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.

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

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