Study Protocol

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BI Investigational Product(s):	Not applicable
Title:	Digital Auscultation Test - Development of an Innovative Approach - using modern technologies - to improve the diagnosis of rare lung diseases – expanded data collection Idiopathic Pulmonary Fibrosis
Brief lay title	Not applicable
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Marketing authorisation holder(s):	Study Initiator: Boehringer Ingelheim Pharma GmbH & Co. KG Binger Straße 173 55216 Ingelheim am Rhein Germany
Joint PASS:	No
Research question and objectives:	The aim of this study is the data collection for patients with Idiopathic Pulmonary Fibrosis (IPF) and symptom matched controls to create a database of lung auscultation sounds and basic patient characteristics.

Country(-ies) of study:	Germany
Author:	
Date:	17-Oct-2018
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ACE	Angiotensin-Converting-Enzyme
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
ATS	American Thoracic Society
BI	Boehringer Ingelheim
BMI	Body Mass Index
BP	Blood Pressure
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data Management Plan
DVP	Data Validation Plan
eCRF	Electronic Case Report Form
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in first second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
HRCT	High Resolution Computer Tomography
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
mMRC	modified Medical Research Council
PASS	Post-Authorization Safety Study
PR	Pulse rate
SAE	Serious Adverse Event
SDR	Source Data Review
SDV	Source Data Verification
SOP	Standard Operating Procedure
TCM	Trial Clinical Manager

3. RESPONSIBLE PARTIES

Function	Name / Location
Principal Investigator	Phone:
Team Member Medical Affairs (TM MA)	Business Model & Health Care Innovation (BMHCI)
Co-Team Member Medical Affairs (Co-TM MA)	Business Model & Health Care Innovation (BMHCI)
GPV CT Coordinator	Boehringer Ingelheim Pharma GmbH & Co. KG Pharmacovigilance
Trial Clinical Monitor	
Statistical Analysis	Boehringer Ingelheim Pharma GmbH & Co. KG Biostatistics + Data Sciences
Data Management	Boehringer Ingelheim Pharma GmbH & Co. KG Biostatistics + Data Sciences
Programming	Boehringer Ingelheim Pharma GmbH & Co. KG Biostatistics + Data Sciences
Information Technology	Boehringer Ingelheim USA Corp. IT R&D – Translational Medicine and Epidemiology

4. ABSTRACT

Name of company: Boehringer Ingelheim Pharma GmbH & Co. KG			
Name of finished medicinal product: not applicable			
Name of active ingredient: not applicable			
Protocol date: 26-Jan-2018	**Study number:** 0352-2119	**Version/Revision:** v3.0	**Version/Revision date:** 17-Oct-2018
Title of study:	Digital Auscultation Tool - Development of an Innovative Approach - using modern technologies - to improve the diagnosis of rare lung diseases – expanded data collection - Idiopathic Pulmonary Fibrosis.		
Rationale and background:	Idiopathic Pulmonary Fibrosis (IPF) is a rare lung disease which is difficult to diagnose early. The assessment of "Velcro Crackles" by lung auscultation could be used as a screening tool. Crackles are not specific for IPF; however only in IPF can these be heard throughout the entire inspiration phase.		
Research question and objectives:	The aim of this study is the data collection for patients with Idiopathic Pulmonary Fibrosis (IPF) and symptom matched controls to create a database of lung auscultation sounds and basic patient characteristics.		
Study design:	Single visit study without study medication Targeting two groups of patients, the first group includes patients with a confirmed diagnosis of IPF and the other group includes patients with matched symptoms as control.		
Population:	Patients with a confirmed diagnosis of IPF as well as symptom matched patients Main inclusion criteria: Age ≥ 45 years; for patients with confirmed IPF diagnosis; a clinical diagnosis of IPF within the last 24 months, according to the ATS/ERS 2011 guideline; symptom matched patients – confirmed current condition of asthma, COPD, pneumonia, upper respiratory tract infection or acute bronchitis. Main exclusion criteria: Body Mass Index >30,0 kg/m²		
Variables:	Lung auscultation sounds, patient medical history and relevant patient demographic information		

Name of company: Boehringer Ingelheim Pharma GmbH & Co. KG			
Name of finished medicinal product: not applicable			
Name of active ingredient: not applicable			
Protocol date: 26-Jan-2018	**Study number:** 0352-2119	**Version/Revision:** v3.0	**Version/Revision date:** 17-Oct-2018
Data sources:	Lung auscultation recorded by electronic stethoscope; patient medical history and demographic data completed by the physician as well as symptom descriptions by the patient.		
Study size:	• 100 patients with confirmed IPF diagnosis • 100 patients with confirmed current condition of asthma, COPD, upper respiratory tract infection, acute bronchitis or pneumonia Additional 70 patients (30 patients with confirmed IPF diagnosis and 40 with confirmed current condition of asthma, COPD, upper respiratory tract infection, acute bronchitis or pneumonia) in the substudy.		
Data analysis:	Descriptive statistics		
Milestones:	Start of data collection Q2 2018 End of data collection Q1 2019 Final report of study results Q3 2019		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
v2.0	03-Jul-2018	4	Addition of sub-study, update of exclusion criterion on BMI, update of milestone timelines	Addition of sub-study, increase available patient population, adaptation to actual initiation date
v2.0	03-Jul-2018	6	Milestones shifted by 1-2 quarters.	Adaptation to actual start of data collection and addition of sub-study.
v2.0	03-Jul-2018	9.2	Sample size increase from 200 to 250 patients	Addition of sub-study
v2.0	03-Jul-2018	9.2.2.2	Exclusion criterion 4: patients with a Body Mass Index (BMI) >30,0 kg/m² (previously >28 kg/m²)	Increase available of patient population, low impact on recording quality expected
v2.0	03-Jul-2018	9.7	Addition of interim analysis	Addition of sub-study
v2.0	03-Jul-2018	14.2	Addition of sub-study	Addition of sub-study
v.3.0	17-Oct-2018	4, 9, 14.2.3.2	Increase sample size	Re-place patients who were auscultated with wrong version of the firmware of eKuore ONE device
v.3.0	17-Oct-2018	4, 6	Milestones shifted by one quarter.	Prolongation of the sub-study to complete additional recruitment

6. MILESTONES

Milestone	Planned Date
Start of data collection	Q2 2018
End of data collection	Q1 2019
Final report of study results	Q3 2019

7. RATIONALE AND BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a progressive, life-threatening, interstitial lung disease of unknown aetiology. The median survival of patients with IPF is only 2 to 3 years [R11-2587] after the diagnosis has been established/confirmed. Diagnosis of rare lung disease like IPF still represents a significant challenge for patients and physicians.

Symptoms precede diagnosis by a median of 1 to 3 years with progression of asymptomatic to symptomatic IPF may occur over years to decades [R11-2587]. Reasons for diagnosis delay may include patient-dependent factors (e.g. reluctance to acknowledge symptoms that may herald health problems and a sedentary lifestyle masking dyspnoea at exercise), disease dependent factors (e.g. progressive onset and slow progression of IPF allows the disease to go undetected/un-diagnosed unless exacerbations occur), and physician-dependent factors (e.g. lack of awareness of rare diseases by general practitioners and even by lung specialists) [P12-10276].

A swift and accurate diagnosis is imperative, especially as treatment initiation at a relatively early disease stage may have the greatest impact on reducing disease progression [R12-3657]. Careful lung auscultation combined with medical history and demographics support differential diagnosis in lung diseases.

7.1 MEDICAL BACKGROUND

Analysis done based on healthcare claims data of a large health plan in the United States yielded a prevalence estimate for IPF of between 14.0 and 42.7 per 100,000 persons [P11-07084].

Early diagnosis of IPF is difficult due to several reasons [R17-2783]: Non-specificity of clinical symptoms at onset (non-productive cough, exertional dyspnoea), functional evaluations do not add to specificity of clinical suspicion, in addition, lung volume can remain unaltered if there is a concomitant emphysema, an association that can be justified by smoking exposure, which represents a common risk factor for both disorders.

It was proposed by several authors [P12-10276] that assessment of “Velcro Crackles” by lung auscultation could be an appropriate method for speedy, early diagnosis of IPF, potentially to be used as a screening tool.

During lung auscultation, a specific sound defined as Crackles, characterized by discontinuous, interrupted explosive sounds, loud, low in pitch are generally attributed to a rapid succession of explosive openings of small airways that closed prematurely during the previous expiration. Crackles have been subdivided according to their timing during inspiration (early or late) and by differences in their quality (“wet” or “dry”).

Crackles are not specific for IPF, and may occasionally be – also – heard in healthy individuals, over the anterior chest, because of closure of small airways in dependent areas of the lungs; however, these usually disappear after several deep breaths [P12-10276]. Follow-

up of asymptomatic patients with Crackles can also reveal occurrence of congestive heart failure. Crackles may also be heard occasionally in patients with chronic obstructive pulmonary disease or bronchiectasis, probably due to greater traction forces being exerted on the small airways. However, Crackles in IPF are heard throughout the entire inspiration phase of the breathing cycle. Adventitious sounds associated with heart failure and pneumonia are higher in frequency and quite distinctly different from fine Crackles of IPF, and rales are present in only one in four patients with left heart congestion due to systolic heart failure.

7.2 RATIONALE FOR PERFORMING THE STUDY

The aim of this study is to generate and collect clinical data of lung auscultation sounds and patient characteristics for patients with Idiopathic Pulmonary Fibrosis (IPF) and symptom matched controls. The data will be included in a project database focusing on lung auscultation sounds combined with relevant demographic information and symptom descriptions by the patients. In addition to data from the current study, the project database will also include data from healthy volunteers [c19451379] and additional fibrotic patients from a collaboration project [R17-4022].

Using this project database it is intended to develop, evaluate and validate a novel algorithm to classify IPF patients against non IPF patients. Such novel tool, once validated, will be able to aid physicians in IPF screening.

The need for the generation of additional new data emerges from the specificity of the lung auscultation protocol.

7.3 BENEFIT - RISK ASSESSMENT

There is no expected individual benefit for the study patients, as all patients are required to have a confirmed diagnosis of their disease.

Overall benefit is expected for future diagnosis and screening, supporting medical practice.

As the lung auscultations are going to be performed with a slightly longer duration than during a “routine examination”, in order to acquire high quality digital sound recordings, a small risk of transitory dizziness due to a hyperventilation should be considered as a potential adverse event during the recording procedure, requiring usual preparation for supporting the patient, if needed during the examination.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this study is the data collection for patients with IPF and symptom matched controls to create a database of lung auscultation sounds and basic patient characteristics.

9. RESEARCH METHODS

9.1 STUDY DESIGN

Single visit for each study participant to record lung auscultation sounds and assess their vital signs, i.e. heart rate, blood pressure, etc. – see Section 9.2.3 for details.

This is a single visit, multi-centre study without any study medication or invasive procedure. The study is designed to collect recordings of lung auscultation sounds, as well as demographic and symptom information of two patient groups (IPF patients versus symptom matched controls).

Patients will be grouped based on their diagnosis at screening.

The end of the study is defined as when the last patient completes the visit.

Additionally a sub-study is planned to collect sound recordings using two different electronic stethoscopes sequentially from approximately 70 additional patients (see Section 14.2).

9.2 SETTING

9.2.1 Study sites

It is planned to collect sounds from approximately 200 patients from 10-12 specialized ILD centres, known to Boehringer Ingelheim from previous IPF studies. Due to the fact that IPF is a rare disease, the study focuses on specialized clinics with clinical study experience with Boehringer-Ingelheim as Sponsor in order to collect high quality data.

The additional sub-study is planned to collect sound recordings from approximately 70 additional patients from 6 of the above mentioned study sites.

9.2.2 Study population

The study population consists of patients with a confirmed diagnosis of IPF and patients with similar symptoms to have a symptom matched control group:

- patients with confirmed IPF diagnosis (N=100 in the main study and N=30 in the sub-study)
- patients with a confirmed current condition of asthma, COPD, upper respiratory tract infection, acute bronchitis or pneumonia as a symptom matched control group (N=100 in the main study and N=40 in the sub-study)

Enrolment will be competitive and the study will be closed when the planned number of patients has been reached. As no interactive response tool will be used in this study, each investigational site must notify the sponsor whenever a patient is enrolled. Therefore a

notification form will be provided by the sponsor. To maintain a balance between IPF and matched control patients, sites should not recruit more matched control patients than IPF patients in the timeframe of a month. Permission to recruit more than 40 patients in total (including sub-study) or to focus on one of the patient groups must be obtained from the TCM at Boehringer-Ingelheim. This will only be allowed after a careful review of the enrolment status and data quality.

9.2.2.1 Inclusion criteria

1. Male or female patients
2. Age ≥ 45 years at the day of the study visit
3. Diagnosis:
   a) For patients with confirmed IPF diagnosis - a clinical diagnosis of IPF within the last 24 months from the day of the study visit, according to the ATS/ERS 2011 guideline [P11-07084]
   or
   b) For the symptom matched control – patients without a IPF diagnosis but with one of the confirmed current conditions as:
      i. asthma diagnosed according to GINA guidelines,
      ii. COPD diagnosed according to GOLD guidelines,
      iii. pneumonia,
      iv. upper respiratory tract infection, or
      v. acute bronchitis.
4. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the study

9.2.2.2 Exclusion criteria

1. Any other current respiratory condition other than the pulmonary disease which qualified the patient eligibility based on inclusion criterion 3
2. Any condition, according to investigator's assessment, which will not allow the patient to comply with protocol assessments or need a legal representative
3. Patients with a history of lobectomy, pneumonectomy or lung transplant
4. Patients with a Body Mass Index (BMI) >30,0 kg/m²
5. Previous enrolment in this study
6. Women who are pregnant

A log, documenting all patients who have been invited for study participation, will be maintained in the study file, recording basic patient characteristics (e.g. gender, year of birth) as well as information on informed consent (enrolment date) and eligibility (or reasons for non-eligibility). A record of all patients who have been invited for study participation at the study site should maintained, irrespective of whether the patient has been enrolled or whether auscultations have been recorded or not.

9.2.3 Study visits

Patients will be enrolled consecutively. The respective assessments and data to be collected are listed in Table 9.2.3: 1. All data will be collected during one visit, no follow-up visit is planned.

Table 9.2.3:1 Visit flow chart and data collection parameters (for the visit flowchart for the substudy see Table 14.2.3.1:1)

Assessments	**Visit 1**
Informed consent[1]	X
Demographics	X
Medical history	X
Review of in-/exclusion criteria	X
Physical examination (including height and weight)	X
Vital signs including blood pressure	X
12-point lung auscultation	X
Symptom questionnaire	X
Adverse events recording	X

[1] Prior to any study related procedure.

9.2.4 Study discontinuation

Patients may potentially be withdrawn from study procedures, but every effort should be made to keep the patients in the study.

Measures to control the withdrawal rate include careful patient selection and appropriate explanation of the study requirements and procedures.

The decision to withdraw from the study as well as the reason must be documented in the patient files and Case Report Forms (CRF).

9.2.4.1 Withdrawal of consent for study participation

Patients may withdraw their consent for study participation at any time without the need to justify the decision.

9.2.4.2 Discontinuation of the study by the sponsor

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1) Failure to meet expected enrolment goals overall or at a particular study site
2) Emergence of any safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the study
3) Violation the study protocol, or the contract impairing the appropriate conduct of the study

The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

9.3 VARIABLES

The following parameters will be collected and assessed:

- Patient demographics (age, gender, height, weight & body mass index)
- Smoking status (current smokers, former smokers, and never smokers) and pack-years
- IPF patients: Patient-reported date of first symptoms; date of IPF diagnosis was confirmed according to ATS/ERS 2011 guideline; method of confirmation (e.g. HRCT, biopsy); family history of IPF
- Symptom matched control: confirmed diagnosis and date of diagnosis
- Relevant current concomitant diseases/therapies potentially affecting auscultation, including specifically congestive heart failure and use of ACE inhibitors.
- Past treatments/surgical interventions which potentially affect lung auscultation
- Date and location of lung biopsy
- Vital signs –blood pressure (systolic and diastolic) and pulse rate
- Spirometry data, if available from prior examination – FEV_1, FVC
- A one page abbreviated paper based questionnaire regarding symptoms experienced by the patient (dyspnea, sputum and cough)
- Weight loss in past 4 weeks;
- Occurrence of heartburn; clubbing of fingers
- 12-point auscultation – recording of sounds in 3M Littmann StethAssist software
- Safety reporting – adverse events (see Section 11)

9.3.1 Exposures

No study medication is used in this study.

There are no restrictions on the use of concomitant medication in this study.

9.3.2 Outcomes

There are no specific endpoints or outcomes on patient level. The aim of this study is the data collection only, the analysis (generation of the algorithm) will be completed on project level.

9.4 DATA SOURCES

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and study records that include all observations and other data pertinent to the investigation on each study patient.

Medical records collected through routine clinical care will be used to assess the inclusion/exclusion criteria of patients. Such medical records will be used for patient demographics, smoking history, diagnosis of IPF, asthma, COPD, upper respiratory tract

infection, acute bronchitis or pneumonia, relevant medical history (including surgeries and biopsy), as well as spirometry data.

Systolic and diastolic blood pressure (BP) and pulse rate (PR) should be measured after the patient has rested for at least 5 minutes in a supine position.

The investigator will use the modified Medical Research Council (mMRC) scale to assess the breathlessness state of the patient, as well as document the patient response to four questions related to the cough symptoms reported by the patients, as well as three questions related to sputum. Answers will be documented in the source transcribed by site staff into the eCRF.

Clubbing of fingers, heartburn, and weight loss will be assessed by yes/no questions, for weight loss, a percentage will be collected, if applicable.

For this study, a 12-point patient auscultation is required. In each defined region of the patient's body, auscultation should be performed to maximize the sound quality according to the investigator's experience as well as instructions in appendix 1. Site staff will receive hands-on training on the use of the stethoscope and the required software during site initiation. Manuals provided by the manufacturer will available in the site file. Auscultations will be recorded using a Littman Digital Stethoscope (Model 3200) and the 3M Littmann StethAssist software on a computer provided for the study.

All related AEs, serious and non-serious associated with the digital Auscultation as well as all related adverse events (ADRs) (serious and non-serious) and all AEs with fatal outcome associated with BI products administered for indication IPF, COPD, asthma must be documented in the patient source documentation and reported to the sponsor, see Section 11 for details.

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

All patients will be enrolled consecutively

9.5 STUDY SIZE

The sample size determination for this study is based on feasibility constraints that IPF is a rare disease and due to the explorative nature of the novel algorithm development which will be conducted at project level.

9.6 DATA MANAGEMENT

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. The Case Report Forms (CRFs) will include programmable edits to obtain immediate feedback if data are missing (also negative answers, unknown), out of range, illogical or potentially erroneous. These rules may encompass simple checks such as range validation or presence/absence of data. Concurrent

manual data review may be performed based on parameters dictated by the DMP. A risk based source data review (SDR) and source data verification (SDV) process will be implemented, Details of the process will be specified in a separate monitoring manual.

The database will be housed in a physically and logically secure computer system. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling and the safety requirements of the FDA (US Food & Drug Administration) concerning systems for the data acquisition of clinical studies in accordance with "Title 21 Code of Federal Regulations (21 CFR Part 11): Electronic Records; Electronic Signatures" Patient confidentiality will be strictly maintained.

9.6.1 Data Entry

Data will be entered into an electronic CRF (eCRF) provided on a study laptop to the sites.

The final CRFs will be approved by the responsible principal investigator within the electronic data capture system.

The data review and validation steps for the study are defined in the data validation plan (DVP).

The DVP includes all definitions of electronic checks and the defined manual checks, which will be performed directly in the eCRF or can be based on listings.

Electronic edit checks (eChecks) are performed automatically and directly when entering data into the CRF. Missing data entries or implausibilities are indicated to the user immediately.

Manual Checks are applied to verify the entered data validity and plausibility.

Queries can result from various sources:

- Manual Checks by data management
- Manual Checks by pharmacovigilance
- Source data review and verification during on-site monitoring

9.6.2 Source Documents

The source documents are contained in the patient's medical record. Data collected in the eCRFs must be traceable to these source documents in the patient's medical records as far as this is routine documentation. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The site will be instructed to notify the Sponsor before any destruction of medical records of study participants.

9.6.3 File Retention and Archiving

The study database and all study-specific documents will be archived by BI Pharma in accordance with BI SOPs.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agrees to keep records, including the identity of participating patients, copies of all CRFs, SAE forms, source documents and adequate documentation of relevant correspondence (e.g. letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the study and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least ten years after the completing participation in the study. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the Sponsor.

9.7 DATA ANALYSIS

All variables mentioned in Section 9.3 will be presented descriptively.

Characteristics of the analytical methods for the analysis will be given in further detail in the study report or in a separate technical report.

An interim database lock will be conducted after the 200 patients of the initial main study have completed the study to provide early access for the explorative tests in the development of the classifying algorithm.

A study report describing all data collected within this study will be produced after the last patient has completed the study.

Handling of missing data

Missing data will be described in the descriptive statistics without imputation.

9.8 QUALITY CONTROL

To improve and secure data quality of the collected auscultation sounds, sounds will be reviewed centrally to ensure high quality standards and to label defined features of the recordings for further analysis in the algorithm generation process based on a detailed guidance document. Central review and labelling will be started during the conduct phase of the study already to provide feedback to the sites where required.

To improve and secure data quality, automatic data checks upon data entry will be done within the eCRF. In the eCRF, plausible ranges of values for numeric data entries as well as logical data entries and listings will be provided for each entry field. Based on this, checks on completeness and plausibility will be performed upon data entry in the eCRF.

Validity of data entry thus is ensured by integrated validation checks performed by the system, indicating missing or implausible entries to the investigator.

Source data review (SDR) and verification (SDV) is planned to be performed at all sites with enrolled patients. Informed consents and in/exclusion criteria will be checked for all patients. For the SDR/SDV of the remaining data an adaptive risk based approach will be implemented.

9.9 LIMITATIONS OF THE RESEARCH METHODS

There is limited experience with the planned project level analysis using complex data including audio files, therefore the planned sample size is based on operational constraints rather than an elaborate calculation. But the explorative nature of the overall project will allow us to test several mathematical approaches to generate a robust algorithm.

Due to operational constraints we are limited to a strictly defined symptom matched control group, which will not encompass the full range of lung sounds. Expanding the database in a second step to provide data for the further development and evaluation of the algorithm is being considered.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

Onsite monitoring including source data verification will be conducted at all sites enrolling patients. An additional check/ review of the quality assurance of this study can be performed.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via remote data capture.

9.10.2.1 Source documents

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

Data entered in the CRFs 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.

All data need to be derived from source documents.

9.10.2.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration (FDA)). The Clinical Research Associate (CRA) / Clinical Monitor Local (CML) and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

10. PROTECTION OF HUMAN PATIENTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the setting of this study and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study patients against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) according to national and international regulations. The same applies for the implementation of changes introduced by amendments. In addition, every participating physician is to be advised by his/her ethics committee in accordance with the rules of professional conduct.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Quality Medicine auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities, i.e. the competent authority.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event is defined as any AE which

- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect.

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are 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 dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator must collect and document in the eCRF from signing the informed consent onwards until the patient´s end of the study:

- all related AEs, serious and non-serious associated with the digital Auscultation

The investigator must report:

- all related adverse events (ADRs) (serious and non-serious)
- all AEs with fatal outcome

associated with BI products administered for **indication IPF, COPD, asthma**

All related AEs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE reported by a patient or observed otherwise constitutes an ADR using the information below.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest a reasonable causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
- Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Pregnancy

In rare cases, pregnancy might occur in a study. Once a patient has been enrolled into the study, after having taken a BI product used for indication, investigator must report any drug exposure during pregnancy (DEDP) **associated with BI products administered for indication IPF, COPD, asthma**, which occurred in a female patient or in a partner to a male patient to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator by means of the Adverse Event Reporting form provided from signing the informed consent onwards until the end of the study via fax to BI Unique Entry point as specified in the Investigator Site File (ISF).

Type of Report	Timeline
All serious ADRs associated with BI products used for indication IPF, COPD, asthma	immediately within 24 hours
All AEs with fatal outcome in patients exposed to BI products used for indication IPF, COPD, asthma	immediately within 24 hours
All non-serious ADRs associated with BI products used for indication IPF, COPD, asthma	7 calendar days
All pregnancy monitoring forms (DEDP after intake of BI products used for indication IPF, COPD, asthma)	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions, the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the AE reporting form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the AE reporting form.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than BI marketed products in outlined indications under expedited reporting (not in scope of the study) according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the sponsor of the study according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

13. REFERENCES

13.1 PUBLISHED REFERENCES

P11-07084 Raghu G, et al, ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 183 (6), 788 - 824 (2011)

P12-10276 Cottin V, Cordier JF. Velcro crackles: the key for early diagnosis of idiopathic pulmonary fibrosis? Eur Respir J 40 (3), 519–521 (2012)

R11-2587 Ley B, Collard HR, King TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 183, 431 - 440 (2011)

R12-3657 Bois RM du. An earlier and more confident diagnosis of idiopathic pulmonary fibrosis. Eur Respir Rev 21 (124), 141–146 (2012)

R17-4022 Sgalla G, Walsh SLF, Sverzellati N, Fletcher S, Cerri S, Dimitrov B, et al. Correlation between lung sounds and HRCT signs of pulmonary fibrosis: a blinded prospective study. 27th Int Cong of the European Respiratory Society (ERS), Milan, 9 - 13 Sep 2017 (Poster)

R17-2783 Cicchitto G, Sanguinetti CM. Idiopathic pulmonary fibrosis: the need for early diagnosis. Multidiscip Respir Med 8, 53 (2013)

13.2 UNPUBLISHED REFERENCES

c19451379 – Non interventional study Development of an innovative approach - using modern technologies - to improve the diagnosis of rare lung diseases. 0352-2106

14. ANNEX

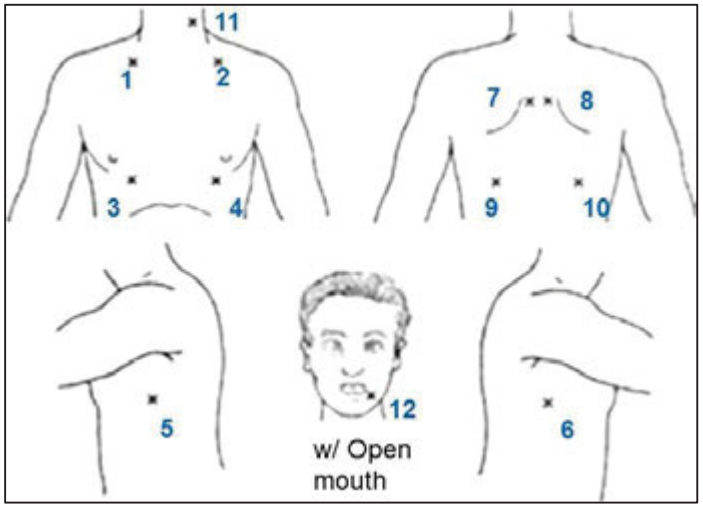
14.1 PATIENT AUSCULTATION INSTRUCTIONS

For this study, a 12-point patient auscultation is required. In each defined region of the patient's body, auscultation should be performed to maximize the sound quality according to the investigator's experience.

Auscultations will be recorded using a Littman Digital Stethoscope (Model 3200) and the 3M Littmann StethAssist software on a computer provided for the study.

- The auscultations should be performed while the patient is standing. If this is not possible due to the condition of the patient (patient not able to stand still for the duration of the auscultations), the auscultations can be performed while the patient is sitting. This should be documented accordingly in the CRF.
- The auscultations should be performed in a quiet room with the least amount of background possible.
- The stethoscope should not be moved during the recording of the auscultation. - if patient has a hairy chest, the investigator should consider wetting the skin of the patient in order to avoid the recording of non-respiratory sounds.
- Patient should breathe with open mouth.
- Patient should perform maximum exhalation, followed by maximum inspiration.
- At each auscultation point breathing should be recorded for 15 seconds.
- The 12 auscultation points should be recorded as shown in Figure 14.1: 1 – the actual location can be recorded in software provided to record the sounds, any deviations should be recorded in the CRF.
- If the patients experiences an intensive fit of coughing the recording of the auscultation point should be stopped and repeated.
- All recordings for a patient should be recorded in one continuous session, on the same day.
- If auscultation results in any abnormal sound, the investigator should describe the location of the auscultation, patient position and characteristics in the CRF.

Figure 14.1: 1 Auscultation Points used and Recording Sequence



14.2 SUB-STUDY –STETHOSCOPE WITH SIMILAR CHARACTERISTICS

14.2.1 Rationale and Background

The main study is limiting the electronic stethoscope used to record the auscultation sounds to one device only, the Littmann 3200. Based on recent developments there are other devices available that have acoustic recording characteristics that are very similar to the Littmann 3200. Therefore there is a need to evaluate whether the recording device used has an impact on the performance of classification algorithms developed based on recordings using the Littmann 3200.

14.2.2 Research Question and Objectives

The aim of this sub-study is the collection of auscultation recordings for patients with IPF and symptom matched controls using two different approved stethoscopes with similar characteristics (Littmann 3200 and Ekuore One) on the same patient to ensure the neutrality of the algorithm regarding the recording device.

14.2.3 Research Methods

14.2.3.1 Sub-study design

After the completion of all assessments from the main study, and a 10 minute break, a second 12-point auscultation using the Ekuore One attached to a Littman Cardiology stethoscope will be completed (see Table 14.2.3.1:1).

Table 14.2.3.1:1 Sub-study flow chart and data collection parameters

Assessments	**Visit 1**
Informed consent including consent to participate in sub-study[1]	X
Demographics	X
Medical history	X
Review of in-/exclusion criteria	X
Physical examination (including height and weight)	X
Vital signs including blood pressure	X
12-point lung auscultation using Littmann 3200	X
Symptom questionnaire	X
12-point lung auscultation using Ekuore One	**X**
Adverse events recording	X

[1] Prior to any study related procedures.

14.2.3.2 Selection of study population

This sub-study will enrol patients from approximately 6 study sites participating in study 0352-2119. Approximately 70patients who gave consent to both the main study and the sub-study will be enrolled into the sub-study. The sub-study should include a sample of approximately 30 IPF patients and 40 symptom matched controls as defined in the main study.

14.2.3.2.1 Inclusion criteria

1. Patients who have provided informed consent to participate in the main study 0352-2119 as well as this sub-study prior to any study related procedures.
2. Patients who have been confirmed as meeting all in- and exclusion criteria (Section 9.2.2.1 and Section 9.2.2.2).

The log of all patients participating in the study should include a clear indication whether the patient participated in the substudy or not.

14.2.3.3 Variables

In addition to the main-study the following parameters will be collected and assessed:

- 12-point auscultation – recording of sounds using the Ekuore One stethoscope

14.2.3.4 Data sources

For this sub-study the same assessments will be performed as in the main study (Section 9.4). Following the auscultation using the Littmann stethoscope, and a 10-minute break, another 12 point auscultation using the Ekuore One will be performed following the same instructions (Section 14.1) but using different software for recording. Both recordings should be performed under the same conditions.

The Ekuore One device will be attached to a Littman Cardiology stethoscope. The auscultations will be recorded using an application on a mobile device provided for the study.

Site staff will receive hands-on training on the use of stethoscope and the required software. Documentation provided by the manufacturer will be available in the site file.

14.2.3.5 Study size

The sample size determination for this study is based on feasibility constraints that IPF is a rare disease and the explorative nature of the project.

14.2.3.6 Data analysis

All variables mentioned in Section 9.3 and 14.2.3.3 will be presented descriptively. A comparison of Littmann 3200 and Ekuore One is outside of the scope of this study and the project.

Characteristics of the analytical methods for the analysis will be given in further detail in the study report or in a separate technical report.

APPROVAL / SIGNATURE PAGE

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Title: Digital Auscultation Test - Development of an Innovative Approach - using modern technologies - to improve the diagnosis of rare lung diseases – expanded data collection Idiopathic Pulmonary Fibrosis

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		17 Oct 2018 13:46 CEST
Author-Trial Statistician		17 Oct 2018 15:20 CEST
Verification-Paper Signature Completion		17 Oct 2018 16:21 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed