OBSERVATIONAL PLAN

Non-interventional study

Study title:

Outpatient care with long-acting bronchodilators:
COPD Register in Germany

Study No.: CNVA237ADE01

Protocol version 0.0 of 02.08.12

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1. Introduction

COPD (chronic obstructive pulmonary disease) is a progressive disease characterised by not fully reversible obstruction of the airways. It is the fourth most common cause of death worldwide at present, with rising tendency (2). The prevalence of COPD in Europe and North America is estimated to be at least 10% of the population over the age of 40 years. In Germany the prevalence is in fact 13.2% according to the BOLD study (3). Dyspnoea, limited physical capacity and gradual social isolation are factors that considerably impair the lives of the patients concerned. At the same time, COPD promotes the development and progression of diabetes and cardiovascular diseases – and vice versa.
Currently there are a number of hypotheses concerning the pathogenesis of COPD. They range from a pulmonary inflammation induced by noxae to changes in the area of the endothelium of the pulmonary arteries, as far as autoimmune phenomena (4).
The strategy to date, whereby the staging of patients with COPD into different categories ensues according to FEV1 impairment only, is not sufficient.

The new position paper produced by the GOLD Committee (2) has therefore recommended that staging should be based initially on the clinical symptoms using the mMRC (modified Medical Research Council) questionnaire on dyspnoea or the CAT (COPD Assessment Test) questionnaire. Secondly, the risk of exacerbation is stratified: this can be done either by counting the number of exacerbations in the last 12 months (<2 = low risk, ≥2 = high risk), or by using a pulmonary function test to determine the airflow restriction and classifying the result as GOLD 1-4 (GOLD 1-2 = low risk, GOLD 3-4 high risk). If both methods of assessment have been applied and their results are contradictory, then the higher risk is taken in each case to determine the COPD severity A-D (see Figure 1) (2).

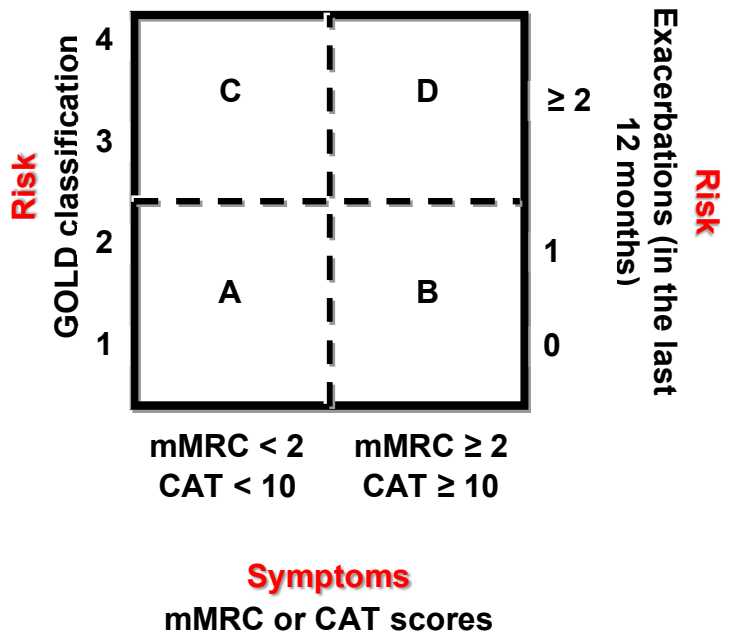

Figure 1: COPD classification as per GOLD (2)

Standard pharmacological therapy for COPD at present still focuses on dilating the bronchi and reducing hyperinflation of the lungs. Current guidelines recommend short or long-acting bronchodilators as basic therapy. This is a symptomatic treatment that uses two classes of substance: beta-2 sympathomimetics which increase the cellular cAMP concentration by stimulating the beta-2 receptors and thus induce bronchospasmolysis, and muscarinic acetylcholine receptor antagonists which block the effect of acetylcholine on the muscarinic receptor and thus lead to expansion of the bronchi.

In addition to numerous short-acting substances for acute treatment (e.g. salbutamol and ipratropium), two long-acting beta-2 sympathomimetics (formoterol and salmeterol) are currently available, as well as an ultra-long-acting beta-mimetic (indacaterol) and an ultra-long-acting anticholinergic agent (tiotropium). All products have a positive effect on the pulmonary function (FEV1, RV), subjective dyspnoea and quality of life of the patients.

Pharmacological research is ongoing into the further development and improvement of the substances already available in terms of efficacy and tolerability. For instance, indacaterol has been available in Germany since 2009 and was the first beta-2 agonist to provide 24-hour bronchodilation in the treatment of COPD. Indacaterol is administered once daily via a single-dose dry powder inhaler. The same inhaler is used to administer the new 24-hour anticholinergic agent, glycopyrronium bromide, marketing authorisation of which is anticipated in the second half of 2012. In studies to date, glycopyrronium has proven to be an effective and tolerable bronchodilator (5-7). Clinical trial data suggest that glycopyrronium

bromide rapidly takes effect, since just 5 minutes after inhalation the FEV1 measurement had improved by 93 mL as compared to the measurement before inhalation (5).

Randomised clinical trials often represent a selective patient population, however, rather than reflecting the real situation faced by many patients. In everyday practice, for example, COPD patients often exhibit numerous comorbidities - a constellation that is avoided as a rule in clinical trials. Patients who frequently experience exacerbations are often excluded from studies, meaning that mostly very little is known about these patients.

This observational study therefore aims to identify and characterise the largest number of COPD patients as possible in clinical practice, and highlight the therapeutic effects particularly of new and innovative medicinal products in Germany. In doing so, the benefit of glycopyrronium bromide therapy should be examined in particular.

2. Objectives of the Register

The primary objective of this study is to document, describe and optimise the diagnosis and treatment of patients with COPD while paying special attention to the individual treatment outcome (glycopyrronium bromide therapy versus an established DMP), as measured by treatment compliance, symptoms and patient-related endpoints. Further objectives are incorporated in a structured approach, whereby

- study inclusion is to be considered in every consecutive patient with COPD undergoing pharmacological antiobstructive therapy and receiving outpatient care at the participating centre
- exacerbations are to be documented prospectively (number, severity, treatment, time to next exacerbation)
- the implementation of guidelines when diagnosing and administering pharmacological therapy to patients with COPD at the participating centres in Germany is to be evaluated
- diagnostic measures performed during an outpatient visit to the doctor are to be documented
- the pulmonary function is to be evaluated over the course
- the progression of COPD over the course is to be documented
- comorbidities are to be documented
- the safety and tolerability of the treatments are to be documented
- potential differences in the general treatment of COPD between the groups of doctors are to be evaluated
- pharmacoeconomic data are to be evaluated
- the rapid onset of effect of glycopyrronium demonstrated by clinical trials is to be evaluated in the practical setting

- AEs/SAEs are to be recorded and documented

Adverse events occurring during treatment will be documented. Serious adverse events will likewise be recorded and reported. The findings should help towards the better understanding and prediction of the course of COPD under pharmacological treatment and enable a distinction to be made between the various degrees of severity of the disease in routine care (differentiation between GOLD 2010 and GOLD 2011), and help in identifying and applying the best possible form of treatment for the different degrees of severity.
The following general, scientific questions should be addressed and answered during this project:

- What is the current situation in terms of care and treatment for patients with COPD in Germany?
- Which other factors underlie COPD or influence its persistence (comorbidities, risk factors)?
- Which treatment concepts and therapies are used in COPD?
- How do patients with COPD respond to the different therapies?
- How does the severity of COPD influence quality of life?
- How do the clinical parameters and subtypes of COPD change over time (pulmonary function, frequency of exacerbations, pharmacological therapy, etc.)?

The varied clinical pattern and variable course of COPD also justify the question of whether COPD is a homogeneous illness. Based on the clinical characteristics, the question whether such patients represent one or several groups and whether and how these groups change over time should be investigated.

Most epidemiological studies are restricted to one-time cross-sectional studies or at best perform a pre-/post-analysis. Little data are available on repeat studies using identical methods and the same population at a clearly subsequent time point. The care provided to patients with COPD thus far has been inadequate. The data from such a project therefore offer the opportunity to descriptively research the routine care provided to such patients and thus achieve transparency as well as optimisation in terms of the relevant care.

3. Type of Study

This is a prospective, national, multicentre, observational cohort study with a follow-up period of at least two years.

4. Research Project with Potential Benefit to Participants

Every consecutive patient with COPD who is receiving an established antiobstructive drug or glycopyrronium bromide after being started on treatment, or after treatment modification, will be considered for enrolment. The patients will be enrolled in the Register at a ratio of 2 (glycopyrronium bromide) to 1 (established therapy according to DMP) for the purposes of evaluating the therapeutic benefit of glycopyrronium bromide under routine conditions. The aim is to achieve an even distribution of treatment-naive and pre-treated patients in both cohorts. Patients are defined as treatment-naive if they have not yet received any maintenance therapy with long-acting bronchodilators.

During the observation period, all COPD patients undergo routine examinations by the treating doctor. In addition, they will be asked about their health-related quality of life using standardised questionnaires (CAT and mMRC), as well as a newly developed questionnaire (Pro questionnaire). The data obtained will provide insight into the extent of the disease and the potential therapeutic outcome; the data can therefore help in gaining new and more in-depth knowledge concerning outpatient treatment for COPD. Ultimately these data will benefit the patient if they are incorporated in standard therapies. Once the patient has been enrolled in the study, the parameters will again be documented at the first follow-up visit (in about 3 months). The aim of this early collection of data is to document the outcome of the new or modified treatment, while concentrating in particular on the health-related quality of life which could possibly be altered as a result of modifying treatment. Over the further course of the study, details of medication and exacerbations will be documented on a quarterly basis. Comprehensive documentation of all the parameters listed in the overview will ensue at yearly intervals (Table 2).

5. Study Design

5.1. Population

All consecutive patients with COPD should be considered for study enrolment in line with the inclusion criteria if they are receiving established antiobstructive drugs or glycopyrronium bromide after undergoing treatment modification or being started on treatment. In all events the treating doctor must make the therapeutic decision prior to the patient being documented in the Register.

In order to guarantee the best selection under the conditions of a non-interventional study, the patients have to be recruited to the DMP (Disease Management Programme) for COPD when enrolled in the study or fulfil the criteria for recruitment to this DMP.

To obtain sufficient information on the new substance, glycopyrronium bromide, patients will be enrolled in the Register at a ratio of 2 (glycopyrronium bromide) to 1 (established therapy). A total of 6 000 patients are to be enrolled at approx. 400 practices across the country.
The patients must confirm in writing that they agree to study participation. Patients in whom there are doubts concerning their cognitive faculty, or in whom such an ability is lacking, shall not be enrolled in the study. Patients unable or only partly able to give consent likewise will not be enrolled in the study.

The resulting inclusion criteria are:

- Written consent of the patient to participation in the study
- Age: ≥ 40 years
- Diagnosis of COPD by a doctor
- Initiation or modification of pharmacological COPD treatment at the start of the study (visit 0)
- Recruitment to the COPD DMP or fulfilment of the DMP inclusion criteria

Enrolled patients should be monitored for at least two years, hence foreseeable difficulties with following up on a patient entail an exclusion criterion.
The following additional exclusion criteria are to be noted:

- Recruitment to DMP Asthma bronchiale
- Ongoing participation in a randomised clinical trial

5.2. Parameters

Sociodemographic data (e.g. sex, year of birth, current treatment centre) and medical data (e.g. diagnosis, therapy, course) will be documented and stored in pseudonymised format in a secure, non-public database.
At the beginning, all patients are to be documented (visit 0). At the next appointment after about three months (visit 1), the outcome of the treatment modification or new treatment will be evaluated using the health-related questionnaires. Furthermore, changes in medication and exacerbations, hospital admissions and AEs/SAEs will be documented at this visit and the quarterly follow-up visits (visits 2, 3, 5-7) (Figure 2). After one year (visit 4) and two years (visit 8), the parameters will be documented in line with Table 2. Further annual visits after three and four years, respectively, are optional.

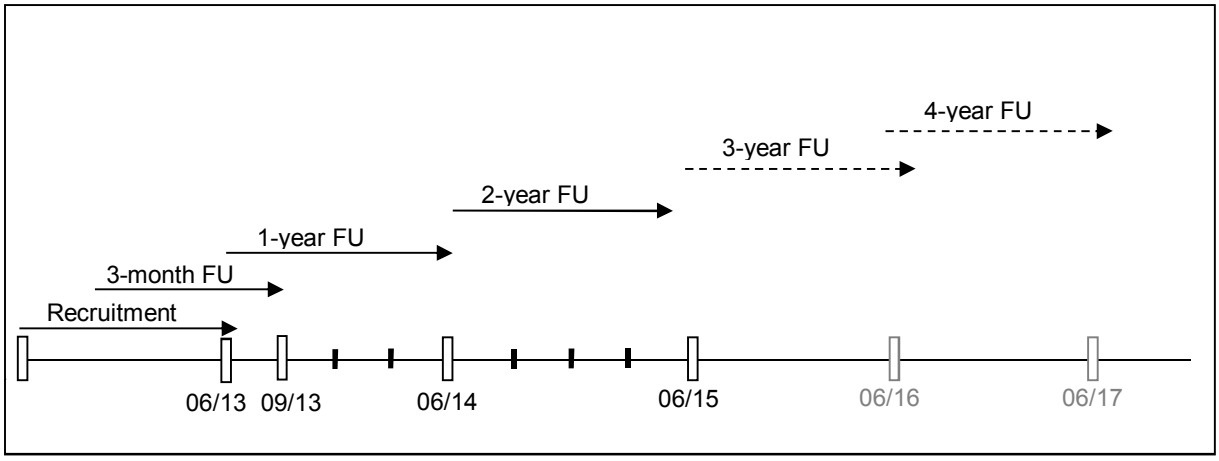

Figure 2: Time schedule

All examinations are based on the national and international recommendations for diagnosis and therapy in patients with COPD and will be performed in accordance with established standards. All visits will be held on an outpatient basis.

The following parameters will be documented in detail (see Table 2):

- Medical history
- Physical examination
- General demographic data
  (year of birth, sex)
- Height, weight, BMI (calculated)
- Smoking status
- Immunisation status (influenza and pneumococci)
- Medication (including non-medical therapy)
- Non-pharmacological treatments
- Comorbidities
- Pulmonary function (spirometry)
- Previous exacerbations
- Safety (AEs/SAEs)

Questionnaires

Questionnaires and surveys will each be conducted or completed by the patient prior to any other examinations or measurements at visits 0, 1, 4 and 8:

- COPD Assessment Test (CAT) – at visit 0, 4 and 8
- Modified Medical Research Council (mMRC) Dyspnoea Scale – at visit 0 only
- Pro (patient-related outcomes) questionnaire – at all visits mentioned above

Pulmonary function (post-bronchodilatory)

Pulmonary function (post-bronchodilatory) should be measured in accordance with the criteria of the ATS (8, 9). Two puffs (200 µg) of salbutamol will be administered for bronchospasmolysis. Pulmonary function will be measured 15 to 30 minutes after administration. A reversibility test should be recorded at visits 0, 4 and 8, if conducted.

5.3. Start and duration of the study, study centres

The study will begin once marketing authorisation has been granted for glycopyrronium bromide in Germany and a positive vote is available from the ethics committee. The recruitment phase is expected to begin in October 2012 and finish in June 2013 (Table 1). A total of 6 000 patients are to be enrolled at 400 practices across the country. The patients will undergo a facultative, initial examination three months after study enrolment and the parameters mentioned above will be recorded. Further examinations will be performed at quarterly intervals in all centres over the next two years (see Table 2).

Observational plan:	
Start of patient enrolment:	On approval of glycopyrronium bromide (expected October 2012)
End of patient enrolment:	June 2013
Start of follow-up:	October 2013
End of observation	June 2015
Final report:	January 2016

Table 1: Start and duration of the study

5.4. Withdrawal criteria

Patients may withdraw their consent to participation at any time, without having to give a reason. Furthermore, the treating doctors may discontinue the observation in an individual patient at any time (e.g. on relocation).

If symptoms increase, treatment will be administered as clinically indicated in accordance with established treatment guidelines. The pharmacological treatment will be adjusted

continuously during the observation period to the course of the COPD at the discretion of the treating doctor, hence no specific reasons for withdrawal are defined. The pharmacological therapy indicated by the COPD guidelines will not be modified for study reasons.

6. Adverse Events

6.1 Definition

An adverse event (AE) is any untoward occurrence in a patient administered a medicinal product, irrespective of whether the reaction is causally related to such treatment (6th Announcement on the Notification of Adverse Drug Reactions and Drug Abuse pursuant to section 63 b paragraph 1 to 8 of the German Medicines Act (AMG), point 2.4). All adverse events that occur with the products documented in the Register (Novartis products, reference products, co-medication) are to be recorded in the eCRF accordingly, by stating the nature of the event, first onset, duration and intensity. Furthermore, information must be provided on whether the event is related to a medicinal product, and if so to which. Reports must also be provided on any countermeasures undertaken and the outcome of the event.

Every adverse event (AE), including side effects and suspected side effects, will be documented. An exception to this rule are exacerbations which the doctor does not believe are causally related to glycopyrronium bromide. An exacerbation is often associated with the progression of COPD, and in phase III studies a significant reduction in the risk of exacerbations could be established for this substance.

In study A2304 as well as study A2303, the time to first exacerbation was significantly prolonged in the case of glycopyrronium bromide for 26 and 52 weeks, respectively, as opposed to treatment with placebo. The percentage of patients with one or more moderate to severe COPD exacerbations was 17.5% and 32.8% for glycopyrronium bromide versus 24.2% and 40.2% for placebo (Kaplan-Meier method). The hazard ratio was estimated at 0.69 [95% CI: 0.500 to 0.949; p = 0.023] and 0.66 [95% CI: 0.520 to 0.850; p = 0.001]. In study A2303, the percentage of patients on tiotropium who experienced a moderate or severe exacerbation was 30.1%. Tiotropium likewise significantly prolonged the time to first exacerbation for 52 weeks [hazard ratio 0.61].
Regarding any change in lung function during the observation period, it will not be charged as clinically relevant, if it is not followed by any intervention.
Serious adverse events (SAEs) will additionally be reported to Novartis Pharma GmbH; refer to the following chapter on adverse events/serious adverse events.

6.2 Serious adverse events

In principle, a distinction must be made between non-serious and serious adverse events.

Serious adverse events (SAEs) are all occurrences that

- are fatal
- are life-threatening
- necessitate hospitalised treatment or prolongation of hospitalised treatment
- result in an incapacity to work*, permanent or serious disability** or invalidity
- result in a congenital anomaly or birth defect
- are medically significant, i.e. have a considerable impact on the patient but do not fulfil any of the above criteria

* incapacity to work is understood here as the consequence of lasting damage to the health

** disability is any serious but temporary, or even permanent impediment, as well as lasting damage.

Hospitalised treatments are not regarded as serious adverse events if one of the following points applies:

- *Hospital stays already* ***scheduled prior to enrolment in the NIS***
- ***Elective hospital admissions*** *for treatment of pre-existing illnesses that are not related to the disease or study medication being examined in the NIS*
- ***Outpatient hospital treatments*** *that do not result in admission (in such a case it is necessary to check, however, whether any of the other criteria apply, e.g. whether the event is life-threatening)*
- ***Hospital treatments*** *that constitute* ***part of the normal treatment or monitoring*** *of the disease being examined in the observational study and which are not caused by a deterioration of the disease*

Progression/exacerbation of the underlying disease **must be reported as an SAE** if it results in **hospitalisation** or fulfils any of the other SAE criteria listed above.

The assessment of whether an SAE applies only depends on whether one of the aforementioned formal criteria applies. ***It is independent of any assessment of the question whether there is possibly a causal relationship between administration of a medicinal product and the occurrence of the SAE***.

All serious adverse events occurring with the products (see above) being documented as part of the Register must not only be entered into the case report form (eCRF) but also be documented **in full in** the additional 'Adverse Event Report' form (which opens automatically

in the eCRF). This report is forwarded automatically as a PDF with additional electronic notification to:

[redacted]

The automatic transmission of the report form is saved under the date and time in the eCRF, whilst other information such as lab results or hospital discharge reports may need to be submitted later upon request. In the event that information on a serious adverse event is of a preliminary nature, such information must be supplemented as soon as possible.

In case of adverse events of **particular interest** (**cardiac events**; e.g. ischaemic heart diseases, cardiac arrhythmias, cardiomyopathies **and events associated with narrow-angle glaucoma**), additional information concerning the event must be documented. After such events have occurred, corresponding questionnaires will be provided by Novartis Pharma GmbH – Department of Drug Safety on a case-by-case basis.

The incidence and the profile of the AEs, ADRs, SAEs, and SADRs occurring during the observation period will be evaluated on the basis of the MedDRA verbatim terms (SOC and PT), version 14.1 (or higher).

Further details are regulated in an additional agreement on handling the Register that accounts in particular for drug safety.

Please note: Adverse events when administering a Novartis medication that are already known to the doctor **before or during the screening examination** and have not yet been reported should be notified irrespective of the procedure mentioned above, by stating the Novartis product(s) taken and offering a causality assessment, to the aforementioned address.

If necessary, there can be obtained a form for this purpose from the given address.

6.3 Exacerbations

All exacerbations should be documented during the observational phase. An exacerbation is defined as a deterioration in the COPD symptoms which

- results in either administration of a systemic corticosteroid or an increase in the existing oral corticosteroid therapy
- and/or necessitates the administration of antibiotics
- and/or requires hospitalisation of the patient
- Any non-serious exacerbation that has occurred with glycopyrronium bromide therapy which is not suspected by the doctor to be causally related to glycopyrronium bromide, does not have to be documented as an adverse event (AE) (see 6.1).

6.4 Pregnancies

Reports of pregnancies during which Novartis products have been used or continue to be used represent important safety information to Novartis that helps to ensure and improve the patient safety in relation to Novartis products.

Any pregnancy during therapy with a Novartis product, irrespective of whether or not it is associated with an AE/SAE, must be reported to the Drug Safety department of Novartis

Fax: [redacted] or [redacted]

within 24 hours of it becoming apparent. The pregnancy must be documented on a separate "Pregnancy Form" and reported to the Drug Safety department of Novartis Pharma GmbH by the treating doctor.

The progress of the pregnancy should be monitored in order to record the outcome of the pregnancy, including any spontaneous and planned terminations, details of the birth and the presence or absence of any birth defects, congenital anomalies or complications in the mother or newborn child.

Such information on the progress of the pregnancy/follow-up information on the birth should be documented on the same 'Pregnancy Case Report Form'.

Every adverse event (AE/SAE) occurring during a pregnancy must be documented additionally in the eCRF in the relevant window for recording 'Serious Adverse Events (SAE)'.

7. Biometrics

7.1 Sample size calculation and population

There are approximately 930 respiratory physicians in Germany. Roughly 300 are likely to participate in this study, corresponding to about 33% of the said group and therefore ensuring representative coverage.
In order to make a comparative analysis of the approaches of different groups of doctors to the treatment of COPD, approximately 100 general practitioners (specialising in pneumology, defined as the possibility to conduct spirometry at the practice) should additionally participate in the study. Roughly 15 patients per centre are expected to be enrolled, producing a total sample size of 6 000 patients. On account of the distribution of the centres and the planned number of patients, a representative picture will be gained of outpatient treatment in Germany for COPD.
Furthermore, because the patient number is large, a number of relevant subsets can be identified and defined (e.g. older patients, women/men, patients with frequent exacerbations, patients with comorbidities, COPD intensities, etc.).

7.2 Analyses

Systematic group differences with respect to prognostic factors must be anticipated in a non-randomised study, leading to distortion from confounding.

In order to still permit comparisons between the two study arms, propensity score stratification will be performed. The main risk factors included therein are age, sex distribution, COPD intensity, smoking status, number of exacerbations, AEs and concomitant diseases. A detailed description will be provided in a separately written statistical analysis plan (SAP); the risk factors to be included therein are still to be defined.

The all-documented patient group covers all patients with at least one entry in the eCRF. The analyses will be differentiated, modelled on randomised clinical trials using the ITT (intend-to-treat) and PP (per-protocol) population.

All the parameters recorded will be analysed descriptively. The qualitative data will be analysed using absolute values and percentages, and the continuous variables presented in a final statistical report using median and quartile values.

The major findings will be summarised in a scientific manuscript and submitted for publication in a peer-reviewed journal.

7.3. Reporting obligations based on PASS status

This study entails a PASS (post authorisation safety study) concept on account of the parameters recorded. The observational plan will therefore be submitted to the European Medicines Agency (EMA) for information prior to study commencement; likewise, the EMA will be notified of all substantial amendments to the observational plan prior to implementation. Annual progress reports will be submitted to the regulatory authorities. The report must contain all relevant data important to the course of the study. This includes, for example, the number of patients enrolled in the Register broken down by status (exposure, outcome, etc.), problems that have occurred, deviations from the observational plan, influence on scheduling and corrective measures undertaken or planned for resolving the problems. Information on the progress of the study is also included in the PSURs (Periodic Safety Update Reports) produced regularly by Novartis, as well as the RMP (Risk Management Plan). The final report will be submitted to the EMA within 12 months after end of the study.

8. Discussion of Ethical and Legal Issues

<u>Consideration of existing laws, regulations and guidelines</u>

The existing laws, regulations and guidelines (refer to the list below) shall be respected and abided by during this study: e.g. the respective paragraphs of the German Medicines Act [AMG] and Medical Device Law [MPG] (as well as appropriate implementing regulations), the

Declaration of the World Medical Association on biomedical research in humans of 1996, the German Professional Code for Medical Doctors, the radiation protection and X-Ray regulations, data privacy laws.

Risks and inconveniences to individual patients

The planned trial is a non-interventional study. Clinically established examinations routinely conducted within the context of outpatient care for COPD patients will be performed at the discretion of the treating doctor. There will be no further risks to the patient related to the examinations.

Patient benefits/study benefits

The results of the tests performed during this project could help to define subpopulations that may benefit from certain forms of treatment, as well as enable statements to be made on the prognosis of COPD patients.

During the observation period, the patients will undergo thorough examination and monitoring for their COPD. The recorded parameters will permit conclusions to be made regarding the extent of the disease and thus may expand the knowledge available, also with a view to compliance with the guidelines. The data obtained could also contribute towards treatment recommendations. Indications of the efficacy or inefficacy of various established COPD therapies could possibly be obtained as part of the study.

Information for patients

The patient will be informed in writing about the nature of the observational study, the procedures and objectives, as well as the handling of their data. A patient informed consent form is enclosed.

Inability to consent

Patients in whom there are doubts concerning their ability to reason, or in whom such an ability is lacking, shall not be enrolled in the study. Patients unable or only partly able to give consent likewise will not be enrolled in the study.

9. Data Protection

All suitable patients will be enrolled in the Register only after receiving comprehensive information and providing written consent. The name, centre number and pseudonym of the patient will be noted on the patient's informed consent. The patient will receive one version of the informed consent, and the other will be retained at the centre. Hence the centre is responsible for assigning the patients and will be able to identify a patient at any time, as well

as contact the patient again for follow-up examinations. Each centre has access to the data of its own patients. The complete database will be stored on the ILF server under the stipulated security measures. After three months, and at yearly intervals, the centre will be automatically reminded to document the patient again. The analysis of the complete database will be performed on a pseudonymised basis. The retention period for study data is 15 years after finalisation of the study report.

These data management procedures comply with the legal data protection requirements applicable at present.

If suspected serious adverse events are reported to be causally related to non-Novartis medicinal products during this non-interventional study, the marketing authorisation holder(s) concerned will be notified by the Drug Safety department of Novartis Pharma GmbH or by the appointed CRO in order that they can fulfil their legal reporting obligations vis-à-vis the authorities. Other marketing authorisation holders may therefore contact the participating doctors with queries concerning the suspected events.

10. Data Management/Electronic Case Report Form/Monitoring

All data will be entered by the participating centres into an Internet-based electronic case report form (eCRF) which has been developed by the study coordinator. The plausibility and completeness of the data are immediately checked in the process, thereby avoiding further queries and erroneous entries as far as possible. Each user at each participating centre is granted individual access to the Internet application. Data are recorded via a secure SSL Internet connection and saved on an ILF server.

The documentation of the data will be checked on-site at about 2% of the centres, the details of which are described in a monitoring plan to be written separately.

11. Quality Control

Plausibility checks are integrated in the database in order to be able to directly detect serious errors during data entry. The person making the entries is then warned of a possible error in the data entered. Random checks for correct data entry will be carried out at 10% of the centres by ILF while guaranteeing data protection.

The patients will be followed up at predefined intervals. To this end, ILF will generate a reminder system which will generate e-mail messages to the respective centres concerning the patients (identification numbers) who again need to be documented.

12. Funding

Funding is provided by Novartis Pharma GmbH.

The participating centres will receive financial compensation to the amount of 70 Euros for each enrolled, fully documented patient at enrolment and 70 Euros for each complete, yearly follow-up (visit 0, 4 and 8). The abridged follow-up at visits 1-3 and 5-7 will be remunerated to the sum of 35 Euros per patient.

13. Literature

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	Visit 0	Visit 1	Visits 2, 3, 5-7	Visits 4 and 8
Study month	**Baseline**	**3 months**	**6, 9, 15, 18, 21 months**	**1 and 2 years**
			'Quarterly visits'	'Annual visits'
Written informed consent	X			
Inclusion/exclusion criteria	X			
Medical History	X			
Physical examination	X			X
General demographics	X			
Height	X			
Weight	X			X
Smoking status	X	X		X
Immunisation status influenza and pneumococci	X			X
Current medication/changes	X	X	X	X
Non-pharmalogical treatment	X			X
Comorbidities	X			X
Pulmonary function test post-bronchodilatory	X			X
Reversibility test	X			X
Exacerbations, incl. hospitalisations	X	X	X	X
CAT questionnaire	X			X
mMRC questionnaire	X			
PRO questionnaire	X	X		X
AEs/SAEs	X	X	X	X

Table 2: Study schedule