


Non-interventional Study Protocol

| | |
|---|---|
| Document Number: | Not applicable |
| BI Study Number: | 1237.51 |
| BI Investigational Product(s): | Not applicable |
| Title: | SATisfaction and adherence to COPD treatment |
| Protocol version identifier: | 1.0 |
| Date of last version of protocol: | 31st July 2015 |
| PASS: | No |
| EU PAS register number: | Not Applicable |
| Active substance: | Not Applicable |
| Medicinal product: | Not Applicable |
| Product reference: | Not Applicable |
| Procedure number: | Not applicable |
| Marketing authorisation holder(s): | Not Applicable |
| Joint PASS: | No |
| Research question and objectives: | <p>Treatment satisfaction in COPD is associated with disease knowledge: subjects who claim to be more informed are more satisfied with their management. Literature data in Italian real world life setting about the relation between treatment satisfaction and clinical parameters are lacking. The present study will explore the patients' satisfaction to COPD medical treatment (i.e. pharmacological and not pharmacological treatment) in a clinical real-world setting and how the satisfaction for medical treatment is related to clinical parameters, quality of life, illness perception and treatment adherence evolution.</p> <p>Moreover health care resource consumption will be observed during the observation period.</p> <p>Primary Objective</p> <p>To describe the patients' satisfaction to COPD medical treatments (by means of the TSQM9) during a 12-month</p> |

| | |
|---|--|
| | <p>observation (namely, at enrolment, after 6 and 12 months) in real-world setting.</p> <p>Secondary Objectives</p> <p>To describe patient disease perception (by means of brief illness perception questionnaire B-IPQ), adherence to COPD treatment (by means of MMAS4), health status (by means of CAT questionnaire) and dyspnea (by means of MMRC) during 12-month observation period.</p> <p>2. To analyse the relation between treatment satisfaction and demographic (such as age and gender) and clinical parameters (such as number of exacerbations and spirometric parameters) and PROs during a 12-month observation period.</p> <p>3. To describe the health care resources utilization and related cost according to the Italian National Health Service (INHS) during 12-month observation period.</p> <p>4. To assess the correlation between patients' satisfaction and resource utilization.</p> |
| Country(-ies) of study: | Italy |
| Author: |  |
| Marketing authorisation holder(s): | Not applicable |
| <i>In case of PASS, add:</i> MAH contact person: | Not applicable |
| <i>In case of PASS, add:</i> <EU-QPPV:> | Not applicable |
| <i>In case of PASS, add:</i> <Signature of EU-QPPV:> | Not applicable |
| Date: | Not applicable |
| <p align="center">Proprietary confidential information</p> <p>© 2015 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved. This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission</p> | |

1. TABLE OF CONTENTS

| | | |
|--------|--|----|
| 1. | TABLE OF CONTENTS..... | 3 |
| 2. | LIST OF ABBREVIATIONS..... | 5 |
| 3. | RESPONSIBLE PARTIES..... | 6 |
| 4. | ABSTRACT..... | 7 |
| 5. | AMENDMENTS AND UPDATES..... | 17 |
| 6. | MILESTONES..... | 18 |
| 7. | RATIONALE AND BACKGROUND..... | 19 |
| 8. | RESEARCH QUESTION AND OBJECTIVES | 21 |
| 9. | RESEARCH METHODS | 22 |
| 9.1 | STUDY DESIGN..... | 22 |
| 9.2 | SETTING..... | 22 |
| 9.3 | VARIABLES | 23 |
| 9.4 | DATA SOURCES..... | 27 |
| 9.5 | STUDY SIZE..... | 28 |
| 9.6 | DATA MANAGEMENT..... | 28 |
| 9.7 | DATA ANALYSIS..... | 29 |
| 9.8 | QUALITY CONTROL..... | 32 |
| 9.9 | STUDY MONITORING..... | 32 |
| 9.10 | GUIDELINES FOR EPIDEMIOLOGICAL STUDIES | 32 |
| 9.11 | CONFIDENTIALITY OF STUDY DOCUMENTS AND SUBJECT RECORDS 32 | |
| 9.12 | INVESTIGATOR'S FILES / RETENTION OF DOCUMENTS | 33 |
| 9.13 | LIMITATIONS OF THE RESEARCH METHODS..... | 33 |
| 9.14 | OTHER ASPECTS | 34 |
| 9.15 | INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS..... | 34 |
| 9.16 | STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT | 34 |
| 9.16.1 | DATA QUALITY ASSURANCE | 35 |
| 9.16.2 | RECORDS | 35 |
| 9.16.3 | SOURCE DOCUMENTS | 35 |
| 9.16.4 | DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS..... | 35 |
| 9.16.5 | STATEMENT OF CONFIDENTIALITY | 36 |
| 9.16.6 | COMPLETION OF STUDY..... | 36 |

| | | |
|--------|--|--|
| 9.16.7 | PROTOCOL VIOLATIONS..... | 36 |
| 9.16.8 | COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY | 36 |
| 10. | PROTECTION OF HUMAN SUBJECTS | 37 |
| 11. | MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS..... | Errore. Il segnalibro non è definito. |
| 11.1 | Definitions of adverse events | Errore. Il segnalibro non è definito. |
| 11.2 | Adverse event and serious adverse event Collection and reporting.... | Errore. Il segnalibro non è definito. |
| 11.3 | Reporting to health Authorities | Errore. Il segnalibro non è definito. |
| 12. | PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS | 42 |
| 12.1 | Operative management of Medical Writing Aspects..... | 42 |
| 12.2 | Ghostwriting and Guest/Ghost Authorship..... | 43 |
| 12.3 | Determining Order of Authorship..... | 43 |
| 13. | REFERENCES | 44 |
| 13.1 | PUBLISHED REFERENCES..... | 44 |
| | ANNEX 1. LIST OF STAND-ALONE DOCUMENTS | 48 |
| | ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS | 49 |
| | ANNEX 3. ADDITIONAL INFORMATION..... | 50 |

2. LIST OF ABBREVIATIONS

| | |
|--------|---|
| AE | Adverse Event |
| BMI | Body Mass Index |
| BIPQ | Brief Illness Perception Questionnaire |
| BITSPA | Boehringer Ingelheim Italy S.p.A. |
| CAT | COPD Assessment Test |
| CI | Confidence Interval |
| CML | Local Clinical Monitor |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTMF | Clinical Trial Master File |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DLCO | Diffusion Lung Capacity for carbon monoxide |
| DMC | Data Monitoring Committee |
| eCRF | Electronic Case Report Form |
| FAS | Full Analysis Set |
| FVC | Forced vital capacity |
| FEV1 | Forced expiratory volume in the 1st second |
| GCP | Good Clinical Practice |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| LTOT | Long-Term Oxygen Therapy |
| MMAS-4 | Morisky medication Adherence Scale, 4 items |
| MMRC | Modified Medical Research Council Dyspnea Scale |
| PRO | Patient Related Outcome |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| TLC | Total Lung Capacity |
| TSQM-9 | Treatment Satisfaction Questionnaire, 9 items |
| VC | Vital Capacity |

3. RESPONSIBLE PARTIES

List of all main responsible parties, including the principal investigators who signed this page, will be kept in a stand-alone document to be listed in Annex 1 and it will be available upon request.

SIGNATURE PAGE

This study protocol has been carefully reviewed and agreed upon by:

Medical [REDACTED]
Boehringer Ingelheim
Milano

[REDACTED] [REDACTED]
05/08/15
Date, signature

Senior Medical Advisor
Boehringer Ingelheim
Milano

[REDACTED] [REDACTED]
05/08/2015
Date, signature

For Contract Research Organization,

Clinical Operation [REDACTED]
[REDACTED]

[REDACTED] [REDACTED]
4/08/2015
Date, signature |

Statistician
[REDACTED]

[REDACTED] [REDACTED]
04/08/2015
Date, signature

4. ABSTRACT

| | | | |
|--|--|---------------------------------|-------------------------------|
| Name of company: Boehringer Ingelheim | | | |
| Name of finished medicinal product: Not applicable | | | |
| Name of active ingredient: Not applicable | | | |
| Protocol date: 31 July 2015 | Study number: 1237.51 | Version/Revision: 1.0 | Version/Revision date: |
| Title of study: | SATisfaction and adherence to COPD treatment | | |
| Rationale and background : | <p>COPD is a debilitating disease characterized by poorly reversible airflow limitation, breathlessness on exertion (1-2), exercise intolerance (3) and limitations in the capacity to perform daily activities (4-5).</p> <p>In studies that have explored patient perspectives regarding the burden and impact of COPD, predominant complaints are shortness of breath and limitations in the ability to participate in activities (6), which negatively impact on social interactions and result in loss of independence (7-8).</p> <p>Patient satisfaction with their medication is shown to affect treatment-related behaviors, such as their likelihood of continuing to use their medication, to use their medication correctly and to adhere with medication regimen (9). Treatment satisfaction may give useful insights not only into the patients' perspective on their current treatment but also about differentiation among alternative treatments. Treatment satisfaction is defined as the individual's rating of important attributes of the process and outcomes of his/her treatment experience (11). It focuses on one aspect of satisfaction with medical care and involves the interaction of expectations, preferences, and satisfaction with medical treatment. Treatment satisfaction assessment is potentially useful for understanding the patient's perspective on their current treatment and can be helpful to differentiate among alternative treatments (14-15). Patient expectations, demographic characteristics, such as age and education, and personal preferences affect treatment satisfaction. The pattern and characteristics (that is, side effects and effectiveness) of ongoing treatments for COPD, and the duration/severity of COPD influence perceptions of treatment satisfaction. More important are the factors most directly connected to the treatment, and the way the treatment is delivered and directly experienced by the patient. Outcomes of treatment, including impact on symptoms and adherence with the treatment regimen, represent an important determinant of treatment satisfaction. In 2012 only the 14.3% of Italian patients affected by obstructive respiratory syndromes was adherent to treatment (48)</p> <p>The complexity, discomfort and convenience associated with treatment also affect patient perceptions and evaluations of satisfaction with the treatment. Finally, the individual's intentions, as manifested by their willingness to continue therapy, or his/her preference for, or choice of the treatment over other alternative treatments are relevant.</p> | | |

| | |
|--|--|
| | <p>Satisfaction to treatment is related to adherence and willingness to continue treatment (16). Almost half of patients with COPD do not adhere to their medications (32).</p> <p>Moreover, the course of COPD can be affected by acute events characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medications, known as exacerbations (33). Despite treatment with maintenance medications, COPD patients continue to have exacerbations, so new medications and disease management interventions are warranted to reduce the severity and frequency of exacerbations and the related cost impact of the disease (34). The COPD assessment test (CAT) is a useful tool for the measurement of the health status during the exacerbation and for evaluation of recovery.</p> <p>Literature data in Italian real world setting about the relation between treatment satisfaction and clinical parameters and PRO are lacking. In a general population survey conducted in ten countries of the Middle East and North Africa region, together with Pakistan on COPD subjects with respiratory symptoms the treatment satisfaction was relatively high, with 83.2% of respondents somewhat or very satisfied with their physician's management. Treatment satisfaction was associated with not having exacerbations and with knowledge, subjects who claimed to be more informed being more satisfied with their management (37).</p> <p>Chronic obstructive pulmonary disease is a major cause of chronic morbidity and mortality worldwide, and its epidemiological, clinical, and socioeconomic impact is progressively increasing. A first estimate of the economic burden of COPD in Italy was conducted in 2008 (the SIRIO [Social Impact of Respiratory Integrated Outcomes] study) (40). Average direct costs and total societal costs in the year before enrollment were €2,932 and €3,291, respectively. Direct cost was €2,461 (hospitalization: €1,570; outpatient: €344; and pharmaceutical: €547) in the first year of follow-up, while total societal cost was €2,707.</p> <p>Patients with COPD are at increased risk for lung infections and other pathologies (eg, pneumonia). A study on two cohorts of 84130 COPD patients each, showed that COPD patients with newly developed pneumonia have higher health care resource utilization and/or costs in all areas explored: hospitalizations, outpatient visits, ER visits, and prescription costs (38). In this study, the pneumonia cohort was approximately nine times more likely to have a hospitalization and four times more likely to have an ER visit during the 12 months of follow-up. A total cost savings of \$22348 was estimated to be associated with the prevention of pneumonia based on the sum of the mean differences of \$14353 in inpatient costs, \$6891 in outpatient costs, and \$1104 in pharmacy costs between the pneumonia and control cohorts.</p> <p>Poor adherence to treatment may contribute to the treatment gap in COPD. A large population-based study have shown that reduced adherence to treatment with tiotropium (TIO) alone or co-administered with fluticasone propionate/salmeterol (TIO + FSC) is associated with increased risk for exacerbations and higher health care utilization in COPD patients (39).</p> |
|--|--|

| | |
|---|--|
| <p>Research question and objectives:</p> | <p>Long-term data on the patients' satisfaction to COPD medical treatments (i.e. pharmacological and not pharmacological treatment) in Italy are scarce. Further, there is limited information on the relation between satisfaction and clinical and patients' parameters. The present study will explore the patients' satisfaction to COPD medical treatment in a clinical real- world setting and how this is related to clinical parameters, quality of life, illness perception and treatment adherence evolution during 12-month follow up.</p> <p>The patients will be also described as far as health status, presence of dyspnea, exacerbation occurrence, patient disease perception and awareness and adherence to COPD treatment during a 12-month follow up. Finally, health care resources utilization and related cost according to the Italian National Health Service during 12-month observation will be estimated and the correlation between patients' satisfaction and resource utilization will be assessed.</p> <p>Primary Objective</p> <p>To describe the patients' satisfaction to COPD medical treatments (by means of the TSQM9) during a 12-month observation period (namely, at enrolment, and after 6 and 12 months) in real- world setting.</p> <p>Secondary Objectives</p> <ol style="list-style-type: none"> 1. To describe patient disease perception (by means of illness perception questionnaire B-IPQ), adherence to COPD treatment (by means of MMAS4), health status (by means of CAT questionnaire) and dyspnea (by means of MMRC) during a 12-month observation period. 2. To analyze the relation between treatment satisfaction and demographic (such as age, gender), clinical (such as number of exacerbations, spirometric parameters) parameters and PROs during a 12-month observation period. 3. To describe the health care resources utilization and related cost according to the Italian National Health Service (INHS) during a 12-month observation period. 4. To assess the correlation between patients' satisfaction and resource utilization. |
| <p>Study design:</p> | <p>This is a multi-center, non-interventional (observational) cohort study based mainly on newly collected data.</p> <p>In 20 Italian Pulmonary Centres about 400 consecutive COPD patients will be enrolled in approximately 8 months (from first patient enrolled). Patients will be followed up for 1 year, with an intermediate evaluation after 6 (+/-1) months from baseline (which is compatible with current clinical practice in Italy for COPD patients management).</p> <p>No treatment will be administered to the patients on the protocol basis, since this is an non-interventional study and the assessment and treatment of the enrolled patients will be applied according to standard clinical practice. The patients switching or stopping treatment during observation period will not be withdrawn from the study. Few patients are expected to stop treatment during study; if any, for primary objective evaluation they will be censored at the latest available visit.</p> |
| <p>Population:</p> | <p>All patients, both female and male gender, referring to pulmonary centers will be</p> |

consecutively enrolled according to the following criteria:

Inclusion Criteria

1. Patients aged ≥ 40 years
2. Patients must have a documented diagnosis of chronic obstructive pulmonary disease (COPD)
3. Patients with no exacerbations in the last 3 months
4. Patients requiring regular treatment according to GOLD guidelines, i.e.: undergoing stable pharmacological treatment for COPD since at least 3 months
5. Written informed consent to both participation in the study and privacy form
6. Patients capable of discernment and able to read or write in Italian language.

Exclusion Criteria

1. Patients who are currently participating in a clinical trial on experimental drugs.
2. Patients naïve to pharmacological treatment for COPD
3. Diagnosis of Asthma COPD Overlap Syndrome (ACOS)

Study Exit criteria

An individual patient may be withdrawn from the non-interventional study prior to completion if any of the following criteria apply:

1. The patient withdraws consent, without the need to justify the decision.
2. The patient is no longer able to participate (according to clinical judgment)
3. Administrative reasons (inclusion in another clinical trial)

| | | | | |
|--|--|-----------------|------------------|--------------------|
| Variables: | Table 1 below is the recommended assessment schedule that most likely mirrors the patterns of routine clinical care of most patients. | | | |
| | Study Visits | Visit 1 | Visit 2 | Visit 3 |
| | | Baseline | Follow-up | Follow-up 2 |
| | Months | 0 | 6 (+/-1) | 12 (+/- 1) |
| | Eligibility criteria Inclusion and exclusion criteria, Informed consent and privacy form | X | | |
| | Baseline information (Socio-)demographic variables: age, gender, race, geographic location, housing situation, marital status, educational and employment status | X | | |
| | Weight, body mass index | X | X | X |
| | Physical examination | X | X | X |
| | Life Habits Smoking (yes/no, number of pack/years, smoke duration) | X | X | X |
| | Medical History/Concomitant diseases. – Charlson Comorbidity Index. | X | X | X |
| | COPD medical history: Date of COPD diagnosis (years from diagnosis); n° of COPD exacerbations/year during the previous year to enrolment visit | X | | |
| | Functional assessment Lung function test results (FEV1, FVC, FEV1 % of the predicted, RV, TLC,DLCO) according to clinical practice | X | X | X |
| | CAT questionnaire | X | X | X |
| | COPD Exacerbations** after enrollment Onset and resolution date Severity (mild, moderate, severe) | X | X | X |
| Disease severity (GOLD 2015Guidelines) | X | X | X | |
| Medications related to COPD, COPD exacerbations and adverse events (LABA, LAMA, | X | X | X | |

| | | | | |
|--|--|---|---|---|
| | SABA, SAMA, ICS/LABA, steroids, antibiotics, etc.): drug, dose, frequency, duration of therapy. - Long-Term Oxygen Therapy (liquid and/or concentrate). | | | |
| | Change of therapy during observation period and reason for change. | | X | X |
| | Non Pharmacological treatment - Pulmonary rehabilitation- | X | X | X |
| | Health-care resource consumption related to COPD, COPD exacerbations and adverse events: <ul style="list-style-type: none"> • Drugs • hospitalization (inward and day hospital) • emergency room access • outpatient visits • GP visits • laboratory tests • clinical examinations | X | X | X |
| | Patient Reported Outcomes Questionnaires/scales | | | |
| | TSQM-9 | X | X | X |
| | MMRC (modified MRC dyspnea scale) | X | X | X |
| | CAT | X | X | X |
| | MMAS-4 (Morisky Medication-Taking Adherence Scale) | X | X | X |
| | Brief Illness Perception Questionnaire | X | X | X |
| | Awareness structured interview | X | X | X |
| | S(AE) assessment | | X | X |
| <p><i>Table 1. Recorded variables.</i></p> <p><i>** An exacerbation will be defined as an increase or new onset of more than 1 symptom (cough, sputum, wheezing, dyspnoea or chest tightness) with at least 1 symptom lasting at least 3 days and leading to patient's attending physician to initiate treatment with systemic steroids and/or antibiotics (moderate exacerbation) or hospital admission (severe exacerbation).</i></p> <p><i>Visit 2 (6+/-1 month), Visit 3 (12+/-1 month) are referred as being the current clinical practice in Italy for COPD patients management.</i></p> <p>Data will be collected at inclusion visit, 6 (±1) and 12 (±1) month follow up.</p> | | | | |

| | |
|--|---|
| | <p>The following questionnaires/scales/patient reported outcomes will be administered to patients. They are briefly described below.</p> <ul style="list-style-type: none">• Treatment Satisfaction Questionnaire, 9 items (TSQM-9);• Brief Illness Perception Questionnaire (BIPQ);• Morisky medication Adherence Scale, 4 items (MMAS-4);• COPD Assessment Test (CAT);• Modified Medical Research Council Dyspnea Scale (MMRC). |
|--|---|

| | | | | | | | | | | | | | | | | | | | | | |
|------------------------------------|---|--------------------|-------------|-------------|--|--|-------------|-----|-----|-----|-----|------------------------------------|-------|-------|-------|-------|---------------------|-------|-------|-------|-------|
| <p>Data sources:</p> | <p>Source data will be medical records usually collected during routine clinical practice other than study-specific questionnaires.</p> <p>Collected variables are defined based on study objectives and according to the non-interventional nature of the study. They consist in data routinely collected in clinical practice, so they are expected to be available in medical charts.</p> <p>For Charlson Comorbidity Index calculation ICD-9CM will be considered by clinical investigators. If ICD-9CM is not available according to routine clinical practice, main ongoing diseases at baseline will be anyway collected.</p> <p>The study data will be collected by means of remote data capture using an electronic case report form (eCRF). Investigators will be provided a user-friendly paper form which is intended as a supportive tool for data collection and will be filled in according to each site specific need (it will not be considered as a source data).</p> <p>Patient-reported outcomes, i.e. scales and questionnaires, will be collected on paper and they will constitute source data.</p> | | | | | | | | | | | | | | | | | | | | |
| <p>Study size:</p> | <p>The sample size was determined on the basis of feasibility criteria. In fact, according to the volume of patients managed by the centres involved in this study, inclusion of 400 subjects (20 patients/center) with the characteristics defined at Inclusion/Exclusion criteria paragraphs is deemed reasonable for the planned enrolment period (8 months). Assuming a drop-out rate ranging from of 5% to 20% (including not evaluable, lost-to follow up and not on treatment patients), effective sample size is expected to range between 320 (drop out=20%) and 380 (drop out=5%).</p> <p>An evaluation of the possible achievable precision of the estimates was performed considering the primary objective of the study. No data on treatment satisfaction is available about COPD patients specifically, therefore available literature data was used as a reference to evaluate possible scenarios. In particular, literature data about TSQM was found on multiple sclerosis, psoriasis, etc, showing the global satisfaction mean score ranging from 54.4 to 79.7 [17,18].</p> <p>Table 2 shows the 95% confidence interval half-width and standard error (SE) of the expected mean of global satisfaction score under different sample sizes.</p> <table border="1" data-bbox="384 1556 1383 1792"> <tr> <td>Expected Mean (SD)</td> <td>54.4 (21.4)</td> <td>79.7 (16.6)</td> <td></td> <td></td> </tr> <tr> <td>Sample Size</td> <td>380</td> <td>320</td> <td>380</td> <td>320</td> </tr> <tr> <td>95% confidence interval half width</td> <td>2.152</td> <td>2.345</td> <td>1.669</td> <td>1.819</td> </tr> <tr> <td>Standard error (SE)</td> <td>1.098</td> <td>1.196</td> <td>0.852</td> <td>0.928</td> </tr> </table> <p><i>Table 2. 95% confidence interval (CI) half-width and standard error (SE) of the expected mean assuming N=380/320 evaluable patients [19]</i></p> <p>In all considered scenarios the relative error of the estimate (CI half-width/expected mean) is lower than 30%. The lower the sample size and the higher the standard deviation, the lower the estimate precision.</p> | Expected Mean (SD) | 54.4 (21.4) | 79.7 (16.6) | | | Sample Size | 380 | 320 | 380 | 320 | 95% confidence interval half width | 2.152 | 2.345 | 1.669 | 1.819 | Standard error (SE) | 1.098 | 1.196 | 0.852 | 0.928 |
| Expected Mean (SD) | 54.4 (21.4) | 79.7 (16.6) | | | | | | | | | | | | | | | | | | | |
| Sample Size | 380 | 320 | 380 | 320 | | | | | | | | | | | | | | | | | |
| 95% confidence interval half width | 2.152 | 2.345 | 1.669 | 1.819 | | | | | | | | | | | | | | | | | |
| Standard error (SE) | 1.098 | 1.196 | 0.852 | 0.928 | | | | | | | | | | | | | | | | | |

| | |
|------------------------------|---|
| <p>Data analysis:</p> | <p>Descriptive analysis will be means, medians, quantiles, proportions (with their respective 95% confidence intervals and SE when relevant) and contingency tables according to the nature of the variables. As a dispersion measurement the standard deviation and the interquartile range will be calculated.</p> <p>The statistical analysis will be done on all evaluable patients i.e. patients who enter the study without inclusion-exclusion criteria violations and with at least one TSQM-9 domain score (effectiveness, convenience and global satisfaction) calculated. Patients with missing values will not be excluded from the analysis, their data will not be replaced; frequency of missing data will be given for all analyzed variables. Lost to follow up patients will be analyzed until their last available visit.</p> <p>The study objectives will be evaluated as described below.</p> <p><u>Primary objective</u></p> <p>The patients' satisfaction for medical treatment will be assessed by the 9-item Treatment Satisfaction Questionnaire for Medication (TSMQ-9) at each study visit (46). It is composed by 3 domains covering efficacy, convenience and global treatment satisfaction. TSQM-9 scores will be calculated according to author's instructions and summarized at each time point on all evaluable patients. Patients lost to follow up will be considered until their last available visit.</p> <p>The patients switching treatment during observation period will not be excluded from analysis and will be evaluated at each visit as above described. Few patients are expected to stop treatment during study; if any, for primary objective evaluation they will be censored at the latest available visit. Comparisons of satisfaction between different treatment/devices are not matter of this study, throughout all analysis treatments will be lumped together.</p> <p><u>Secondary objectives</u></p> <p><u>#1 To describe patient disease perception (B-IPQ), adherence to COPD treatment (MMAS4), health status (CAT) and dyspnea (MMRC) during a 12-month observation period</u></p> <p>A description of B-IPQ, MMAS-4, CAT and MMRC scores will be provided at baseline and at follow-up visits. Scale scores will be summarized at each time point. Patients lost to follow up will be considered until their last available visit. Missing items of questionnaires/scales will be replaced where applicable according to scoring algorithms.</p> <p><u>#2 To analyse the relation between treatment satisfaction for medical treatment and demographic/clinical parameters and PROs during a 12-month observation period</u></p> <p>Three regression models (one for each TSQM-9 domain score) will be estimated; the dependent variable will be domain score and the independent ones will be: age and gender (at enrollment), number of exacerbations, relevant spirometry parameters, level of dyspnea (MMRC score), impact of COPD on a patient's life (CAT) and treatment adherence (MMAS-4 score) collected during observational period. Because dependent variable will be collected at each study visit, repeated measures models will be estimated taking into account all available values for dependent and independent variables.</p> <p><u>#3 To describe the health care resources utilization and related cost during a 12-month observation period</u></p> <p>The health care resources consumption will take into consideration the following</p> |
|------------------------------|---|

| | |
|---------------------------|---|
| | <p>events related to management of COPD and COPD exacerbations: inpatients and outpatients hospitalization (inward and day-hospital), accesses to emergency room, General Practitioner (GP) and outpatient visits, laboratory tests and examinations, pharmacological and non-pharmacological therapies (pulmonary rehabilitation) occurred/administered during study period.</p> <p>Medications for adverse events will be considered too.</p> <p>The annual direct health care resource consumption and related cost will be provided by means of descriptive statistics of the variables mentioned above. In order to describe the health care cost from enrolment up to the end of 12-month follow-up according to the INHS point of view (26), a two steps approach will be followed: (i) first of all the resource consumed since enrolment will be calculated and then (ii) a monetary value will be assigned to the resource consumption.</p> <p>(i) Health care resources consumption exclusively related to COPD, COPD exacerbations and COPD-drug-related adverse events will be computed during observational period in terms of pharmacological and non-pharmacological treatments, number of (inward and day-hospital) hospitalizations, number of emergency room accesses, number of GP visits, specialist visits, laboratory tests or examinations (spirometry, FEV1, FVC, FEV1 % of the predicted, RV, IC, TLC, DLCO).</p> <p>(ii) In order to estimate the economic impact on health care sector related cost (30) of the above mentioned health services (hospital admissions, visits, treatments, examinations, spirometry) consumption, a monetary value to each event recorded will be assigned, as defined by the Italian Ministry of Health through the tariffs in force for outpatient setting (31). The cost of hospitalization will be valued according to the most recent available diagnosis-related group (DRG) tariffs (32); finally, pharmacological treatments will be costed at consumer price. All costs will be expressed in €2015. A monthly (or yearly) cost will be provided by taking into account patients according to duration of observation and parametrizing each patient to the 12-month observation period.</p> <p>Descriptive statistics (mean, standard deviation, median, minimum and maximum) of the annual direct health care resource consumption and related cost will be provided.</p> <p>Non-parametric bootstrap method will be applied to cost data for calculating 95% confidence intervals (22-23).</p> <p><u>#4 To assess the correlation between patients' satisfaction and resource utilization.</u></p> <p>Correlation indexes will be calculated between treatment satisfaction domain scores of TSQM-9 and healthcare resource consumption (such as number of hospitalizations, emergency room accesses, GP visits, laboratory test. etc... during observation period) at 12-month follow-up visit. The patients switching treatment during observation period will not be excluded from analysis and will be evaluated at each visit. The patients stopping treatment during study will be censored at the latest available visit</p> |
| <p>Milestones:</p> | <ul style="list-style-type: none"> - Start of data collection: November 2015 - End of data collection: July 2017 - Final report of study results: December 2017 |

5. AMENDMENTS AND UPDATES

Any change or addition to the protocol requires a written protocol amendment that must be approved by BITSPA and all main responsible parties, the principal investigator and the relevant EC before implementation. Amendments only affecting administrative aspects of the study do not require formal protocol amendments or EC approval but the ECs have to be informed of such administrative changes.

6. MILESTONES

The first patient enrolled in the study is expected in November 2015. The end of the data collection (including the follow-up period) is expected within July 2017, depending on the effective enrolment period necessary to collect data from about 400 consecutive COPD patients to be enrolled in approximately 8 months (from first patient enrolled).

| Milestone | Planned Date |
|--------------------------------|---------------------|
| Start of data collection | November 2015 |
| End of data collection | July 2017 |
| Final report of study results: | December 2017 |

7. RATIONALE AND BACKGROUND

COPD is a debilitating disease characterized by poorly reversible airflow limitation, breathlessness on exertion (1-2), exercise intolerance (3) and limitations in the capacity to perform daily activities (4-5).

In studies that have explored patient perspectives regarding the burden and impact of COPD, predominant complaints are shortness of breath and limitations in the ability to participate in activities (6), which negatively impact on social interactions and result in loss of independence (7-8).

Patient satisfaction with their medication is shown to affect treatment-related behaviors, such as their likelihood of continuing to use their medication, to use their medication correctly and to adhere with medication regimen (9). Treatment satisfaction may give useful insights not only into the patients' perspective on their current treatment but also about differentiation among alternative treatments. Treatment satisfaction is defined as the individual's rating of important attributes of the process and outcomes of his/her treatment experience (11). It focuses on one aspect of satisfaction with medical care and involves the interaction of expectations, preferences, and satisfaction with medical treatment. Treatment satisfaction assessment is potentially useful for understanding the patient's perspective on their current treatment and can be helpful to differentiate among alternative treatments (14-15). Patient expectations, demographic characteristics, such as age and education, and personal preferences affect treatment satisfaction. The pattern and characteristics (that is, side effects and effectiveness) of ongoing treatments for COPD, and the duration/severity of COPD influence perceptions of treatment satisfaction. More important are the factors most directly connected to the treatment, and the way the treatment is delivered and directly experienced by the patient. Outcomes of treatment, including impact on symptoms and adherence with the treatment regimen, represent an important determinant of treatment satisfaction. In 2012 only the 14.3% of Italian patients affected by obstructive respiratory syndromes was adherent to treatment (48).

The complexity, discomfort and convenience associated with treatment also affect patient perceptions and evaluations of satisfaction with the treatment. Finally, the individual's intentions, as manifested by their willingness to continue therapy, or his/her preference for, or choice of the treatment over other alternative treatments are relevant.

Satisfaction to treatment is related to adherence and willingness to continue treatment (16). Almost half of patients with COPD do not adhere to their medications (32). Illness and medication beliefs are important determinants of adherence in COPD. A recent study showed that in an a cohort of adults with COPD from New York and Chicago, concerns about medications (evaluated by means of Brief Illness Perception Questionnaire and the Beliefs about Medications Questionnaire) were associated with non-adherence evaluated by means of Medication Adherence Report Scale (32).

Although guidelines recommend monitoring symptoms in patients with COPD, there is limited information on the longitudinal changes in patient-reported dyspnea (PRD) related to activities of daily living. In a observational cohort study of symptomatic patients with stable COPD evaluated every 6 months for 2 years, PRD scores on the modified Medical Research Council (MMRC) scale demonstrate progression over two years despite stable lung function (36). Moreover, the course of COPD can be affected by acute events characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medications, known as exacerbations (33).

COPD exacerbations have serious negative impact on patient quality of life, lung function, and socioeconomic costs so their prevention, early detection, and prompt treatment have a great importance in the management of the disease. Despite treatment with maintenance medications, COPD patients continue to have exacerbations, so new medications and disease management interventions are warranted to reduce the severity and frequency of exacerbations and the related cost impact of the disease (34). The COPD assessment test (CAT) is a useful tool for the measurement of the health status during the exacerbation and for evaluation of recovery; in an observational, prospective study aimed at assessment of the course of CAT scores during bacterial exacerbations of COPD treated in outpatient setting, a significant improvement in the patient's health status during recovery from exacerbation as compared to their health status at the time of exacerbation was found (35).

Literature data in Italian real world setting about the relation between treatment satisfaction and clinical parameters and PRO are lacking. In a general population survey conducted in ten countries of the Middle East and North Africa region, together with Pakistan on COPD subjects with respiratory symptoms the treatment satisfaction was relatively high, with 83.2% of respondents somewhat or very satisfied with their physician's management. Treatment satisfaction was associated with not having exacerbations and with knowledge, subjects who claimed to be more informed being more satisfied with their management (37). Chronic obstructive pulmonary disease is a major cause of chronic morbidity and mortality worldwide, and its epidemiological, clinical, and socioeconomic impact is progressively increasing. A first estimate of the economic burden of COPD in Italy was conducted in 2008 (the SIRIO [Social Impact of Respiratory Integrated Outcomes] study) (40). Average direct costs and total societal costs in the year before enrollment were €2,932 and €3,291, respectively. Direct cost was €2,461 (hospitalization: €1,570; outpatient: €344; and pharmaceutical: €547) in the first year of follow-up, while total societal cost was €2,707. The therapeutic approach followed in a specialist center, based on the application of clinical guidelines, has been shown to be a highly effective investment for the long-term management of COPD. A small increase of pharmaceutical costs per year allowed a substantial saving in terms of hospitalizations, costs related to outpatient services, and indirect costs.

Patients with COPD are at increased risk for lung infections and other pathologies (eg, pneumonia). A study on two cohorts of 84130 COPD patients each, showed that COPD patients with newly developed pneumonia have higher health care resource utilization and/or costs in all areas explored: hospitalizations, outpatient visits, ER visits, and prescription costs (38). In this study, the pneumonia cohort was approximately nine times more likely to have a hospitalization and four times more likely to have an ER visit during the 12 months of follow-up. A total cost savings of \$22348 was estimated to be associated with the prevention of pneumonia based on the sum of the mean differences of \$14353 in inpatient costs, \$6891 in outpatient costs, and \$1104 in pharmacy costs between the pneumonia and control cohorts.

Poor adherence to treatment may contribute to the treatment gap in COPD. A large population-based study have shown that reduced adherence to treatment with tiotropium (TIO) alone or co-administered with fluticasone propionate/salmeterol (TIO + FSC) is associated with increased risk for exacerbations and higher health care utilization in COPD patients (39).

8. RESEARCH QUESTION AND OBJECTIVES

Treatment satisfaction in COPD is associated with disease knowledge: subjects who claim to be more informed are more satisfied with their management. Long-term data on the patients' satisfaction to COPD medical treatments (i.e. pharmacological and not pharmacological treatment) in Italy are scarce. Further, there is limited information on the relation between satisfaction and clinical and patients' parameters. The present study will explore the patients' satisfaction to COPD medical treatment in a clinical real- world setting and how this is related to clinical parameters, quality of life, illness perception and treatment adherence evolution during 12-month follow up.

The patients will be also described as far as health status, presence of dyspnea, exacerbation occurrence, patient disease perception and awareness and adherence to COPD treatment during a 12-month follow up. Finally, health care resources utilization and related cost according to the Italian National Health Service during 12-month observation will be estimated and the correlation between patients' satisfaction and resource utilization will be assessed.

Primary Objective

To describe the patients' satisfaction to COPD medical treatments (by means of the TSQM9) during a 12-month observation period (namely, at enrolment, and after 6 and 12 months) in real- world setting.

Secondary Objectives

5. To describe patient disease perception (by means of illness perception questionnaire B-IPQ), adherence to COPD treatment (by means of MMAS4), health status (by means of CAT questionnaire) and dyspnea (by means of MMRC) during a 12-month observation period.
6. To analyze the relation between treatment satisfaction and demographic (such as age, gender), clinical (such as number of exacerbations, spirometric parameters) parameters and PROs during a 12-month observation period.
7. To describe the health care resources utilization and related cost according to the Italian National Health Service (INHS) during a 12-month observation period.
8. To assess the correlation between patients' satisfaction and resource utilization.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a multi-center, non-interventional (observational) cohort study based mainly on newly collected data.

In 20 Italian Pulmonary Centres about 400 consecutive COPD patients will be enrolled in approximately 8 months (from first patient enrolled). Patients will be followed up for 1 year, with an intermediate evaluation after 6 (+/-1) months from baseline (which is compatible with current clinical practice in Italy for COPD patients management).

No treatment will be administered to the patients on the protocol basis, since this is a non-interventional study and the assessment and treatment of the enrolled patients will be applied according to standard clinical practice. The patients switching or stopping treatment during observation period will not be withdrawn from the study. Few patients are expected to stop treatment during study; if any, for primary objective evaluation they will be censored at the latest available visit.

9.2 SETTING

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site.

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. Any administrative reasons that could significantly affect continuation of the study according to signed site contract
3. Violation of GCP, the CTP, or the contract by a study site or investigator, disturbing the appropriate conduction 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).

All patients, both female and male gender, referring to pulmonary centers will be consecutively enrolled according to the following criteria:

Inclusion Criteria

7. Patients aged ≥ 40 years
8. Patients must have a documented diagnosis of chronic obstructive pulmonary disease (COPD)
9. Patients with no exacerbations in the last 3 months
10. Patients requiring regular treatment according to GOLD guidelines, i.e.: undergoing stable pharmacological treatment for COPD since at least 3 months
11. Written informed consent to both participation in the study and privacy form
12. Patients capable of discernment and able to read or write in Italian language.

Exclusion Criteria

4. Patients who are currently participating in a clinical trial on experimental drugs.
5. Patients naïve to pharmacological treatment for COPD
6. Diagnosis of Asthma COPD Overlap Syndrome (ACOS)

Study Exit criteria

An individual patient may be withdrawn from the non-interventional study prior to completion if any of the following criteria apply:

4. The patient withdraws consent, without the need to justify the decision.
5. The patient is no longer able to participate (according to clinical judgment)
6. Administrative reasons (inclusion in another clinical trial)

9.3 VARIABLES

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study.

This is a descriptive study, where patients with COPD, who are on treatment, are enrolled and evaluated during 12-months follow-up.

Exposure is defined as having diagnosis of COPD and being under treatment so in this study all enrolled patients are considered exposed.

The treating physician is asked to complete if possible at every patient visit the appropriate CRF.

Primary endpoint will be the patients' satisfaction to COPD medical treatments evaluated through the TSQM9 at baseline and at follow-up visits.

Secondary endpoints will be: patient disease perception (evaluated by means of illness perception questionnaire B-IPQ), adherence to COPD treatment (evaluated by means of MMAS4), health status (evaluated by means of CAT questionnaire) and dyspnea (evaluated by means of MMRC) during a 12-month observation period. Moreover, socio-demographic variables, smoking habits, medical history at baseline and lung function test results (by means of spirometry), COPD exacerbations, disease severity and medications for COPD, COPD exacerbations and adverse events during follow up will be collected. At each visit, each patient will fill in a structured interview aimed at assess his/her awareness of the disease.

Measurements of parameters will be performed by validated questionnaires or widely accepted instruments (e.g. spirometry).

Pulmonary function tests are a validated and well established measurement tool for lung function testing. Pulmonary function tests will be conducted at clinic visits using the site's

own equipment. FEV1, FVC, and DLCO are standard measurements for the assessment of lung function.

Finally, health care resources related to COPD, COPD exacerbations and adverse events will be evaluated during the observation period.

Table 1 below is the recommended assessment schedule that most likely mirrors the patterns of routine clinical care of most patients.

| Study Visits | Visit 1 | Visit 2 | Visit 3 |
|---|----------|-----------|-------------|
| | Baseline | Follow-up | Follow-up 2 |
| Months | 0 | 6 (+/-1) | 12 (+/- 1) |
| Eligibility criteria Inclusion and exclusion criteria, Informed consent and privacy form | X | | |
| Baseline information (Socio-)demographic variables: age, gender, race, geographic location, housing situation, marital status, educational and employment status | X | | |
| Weight, body mass index | X | X | X |
| Physical examination | X | X | X |
| Life Habits Smoking (yes/no, number of pack/years, smoke duration) | X | X | X |
| Medical History and concomitant diseases. - Charlson Comorbidity Index. | X | X | X |
| COPD medical history: Date of COPD diagnosis (years from diagnosis); n° of COPD exacerbations/year during the previous year to enrolment visit | X | | |
| Functional assessment Lung function test results (FEV1, FVC, FEV1 % of the predicted, RV, TLC,DLCO) according to clinical practice | X | X | X |
| CAT questionnaire | X | X | X |
| COPD Exacerbations** after enrollment Onset and resolution date Severity (mild, moderate, severe) | X | X | X |
| Disease severity (GOLD 2015 Guidelines) | X | X | X |
| Medications related to COPD, COPD exacerbations and adverse events (LABA, LAMA, SABA, SAMA, ICS/LABA, steroids, antibiotics, etc.): drug, dose, frequency, duration of therapy. - Long-Term Oxygen Therapy (liquid and/or concentrate). | X | X | X |
| Change of therapy during observation period and reason for change. | | X | X |
| Non Pharmacological treatment - Pulmonary rehabilitation- | X | X | X |
| Health-care resource consumption related to COPD, COPD | X | X | X |

| Study Visits | Visit 1 | Visit 2 | Visit 3 |
|--|----------|-----------------|-------------------|
| | Baseline | Follow-up | Follow-up 2 |
| Months | 0 | 6 (+/-1) | 12 (+/- 1) |
| exacerbations and adverse events: <ul style="list-style-type: none"> • Drugs • hospitalization (inward and day hospital) • emergency room access • outpatient visits • GP visits • laboratory tests • clinical examinations | | | |
| Patient Reported Outcomes Questionnaires/scales | | | |
| TSQM-9 | X | X | X |
| MMRC (modified MRC dyspnea scale) | X | X | X |
| CAT | X | X | X |
| MMAS-4 (Morisky Medication-Taking Adherence Scale) | X | X | X |
| Brief Illness Perception Questionnaire | X | X | X |
| Awareness structured interview | X | X | X |
| S(AE) assessment | | X | X |

Table 1. Recorded variables.

*** An exacerbation will be defined as an increase or new onset of more than 1 symptom (cough, sputum, wheezing, dyspnoea or chest tightness) with at least 1 symptom lasting at least 3 days and leading to patient's attending physician to initiate treatment with systemic steroids and/or antibiotics (moderate exacerbation) or hospital admission (severe exacerbation).*

Visit 2 (6+/-1 month), Visit 3 (12+/-1 month) are referred as being the current clinical practice in Italy for COPD patients management.

Data will be collected at inclusion visit, 6 (±1) and 12 (±1) month follow up.

The following questionnaires/scales/patient reported outcomes will be administered to patients. They are briefly described below.

- Treatment Satisfaction Questionnaire, 9 items (TSQM-9);
- Brief Illness Perception Questionnaire (BIPQ);
- Morisky medication Adherence Scale, 4 items (MMAS-4);
- COPD Assessment Test (CAT);
- Modified Medical Research Council Dyspnea Scale (MMRC).

Treatment Satisfaction Questionnaire for Medication, 9 items (TSQM-9)

Patient's self-reported satisfaction or dissatisfaction with pharmacological treatments can be measured using the Treatment Satisfaction Questionnaire for Medication (TSQM) Version 1.4, a validated instrument (45). The TSQM-9 was derived from the original version, and it has a total of 9 items with responses to nearly all items rated on a five-point or seven-point rating scale that provide scores on three scales: effectiveness (3 items), convenience (3

items) and global satisfaction (3 items) (9) . The original version also recorded information about side effects in 5 items (45). However in naturalistic studies, administering the TSQM with the side effects domain could provoke the physician to assess the presence or absence of adverse events in a way that is clinically atypical, carrying the potential to interfere with routine medical care.

The TSQM-9 domain scores (effectiveness, convenience and global satisfaction) will be calculated as recommended by the instrument authors (45,46). The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain.

The questionnaire will be completed by patients at enrolment, 6- and 12-month follow up visits.

Brief Illness Perception Questionnaire

The patient disease perception will be evaluated by the Brief Illness Perception Questionnaire

(Brief IPQ) that is a validated 9-item questionnaire designed to rapidly assess cognitive and emotional representations of illness (ref Broadbent 2006). All of the questionnaire items (except the causal question, item 9) are rated using a 0-to-10 response scale (17). Five of the items assess cognitive illness representations: consequences (Item 1), timeline (Item 2), personal control (Item 3), treatment control (Item 4), and identity (Item 5). Two of the items assess emotional representations: concern (Item 6) and emotions (Item 8). One item assesses illness comprehensibility (Item 7). Assessment of the causal representation is by an opened response item, which asks patients to list the three most important causal factors in their illness (Item 9).

The questionnaire will be completed by patients at enrolment, 6- and 12-month follow up visits.

Morisky medication Adherence Scale 4 items (MMAS-4)

The MMAS-4 is a self-reported, medication-taking behavior scale and consists of four questions about the way patients might experience drug errors or omissions. Each item has a scoring scheme of “Yes” = 0 and “No” = 1. Items are summed to give a non-adherence score ranging from 0 to 4 (42-44); higher score means better adherence to therapy.

The scale will be completed by patients at enrolment, 6- and 12-month follow up visits.

COPD Assessment Test (CAT)

During the 12-month observation period the COPD symptoms will be evaluated by the COPD Assessment Test (CAT). The CAT is an 8-item unidimensional measure of health status impairment in COPD (41). It is designed to measure the impact of COPD on a person's life, and how this changes over time. It contains eight short, simple, patient-completed questions. Patients can choose a score from 0 to 5 for the extent to which the described impairment is true for them, thereby providing a measure of the impact of COPD on their individual health.

The score ranges from 0 to 40; higher scores represent worse health. The CAT score is calculated as the sum of the responded items.

The questionnaire will be completed by patients at enrolment, 6- and 12-month follow up visits.

Modified Medical Research Council (MMRC) dyspnea scale

The modified Medical Research Council (MMRC) dyspnea scale [44] has been in use for many years for grading the effect of breathlessness on daily activities [45, 46]. This scale measures perceived respiratory disability, the WHO definition of disability being “any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being”. The MMRC dyspnea scale is simple to administer as it allows the physician to indicate the extent to which the breathlessness affects the mobility of the patient.

The scale will be completed by patients at enrolment, 6- and 12-month follow up visits.

The physician will ask the patient about his/her perceived breathlessness and will use the modified MRC dyspnea scale to classify it into MMRC dyspnea grades [44]:

Grade

- 0 Breathless with strenuous exercise
- 1 Short of breath when hurrying on the level or walking up a slight hill
- 2 Walks slower than people of the same age on the level because of breathlessness or stops for breath when walking at own pace on the level
- 3 Stops for breath after walking about 100 meters or after a few minutes on the level
- 4 Too breathless to leave the house or breathless when dressing or undressing

9.4 DATA SOURCES

Source data will be medical records usually collected during routine clinical practice other than study-specific questionnaires.

Collected variables are defined based on study objectives and according to the non-interventional nature of the study. They consist in data routinely collected in clinical practice, so they are expected to be available in medical charts.

For Charlson Comorbidity Index calculation ICD-9CM will be considered by clinical investigators. If ICD-9CM is not available according to routine clinical practice, main diseases ongoing at baseline will be anyway collected.

The study data will be collected by means of remote data capture using an electronic case report form (eCRF). Investigators will be provided a user-friendly paper form which is intended as a supportive tool for data collection and will be filled in according to each site specific need (it will not be considered as a source data).

Patient-reported outcomes, i.e. scales and questionnaires, will be collected on paper and they will constitute source data.

9.5 STUDY SIZE

The sample size was determined on the basis of feasibility criteria. In fact, according to the volume of patients managed by the centres involved in this study, inclusion of 400 subjects (20 patients/center) with the characteristics defined at Inclusion/Exclusion criteria paragraphs is deemed reasonable for the planned enrolment period (8 months). Assuming a drop-out rate ranging from of 5% to 20% (including not evaluable,lost-to follow up and not on treatment patients), effective sample size is expected to range between 320 (drop out=20%) and 380 (drop out=5%).

An evaluation of the possible achievable precision of the estimates was performed considering the primary objective of the study. No data on treatment satisfaction is available about COPD patients specifically, therefore available literature data was used as a reference to evaluate possible scenarios. In particular, literature data about TSQM was found on multiple sclerosis, psoriasis, etc, showing the global satisfaction mean score ranging from 54.4 to 79.7 (17,18)].

Table 2 shows the 95% confidence interval half-width and standard error (SE) of the expected mean of global satisfaction score under different sample sizes.

| | | | | |
|------------------------------------|-------------|-------|-------------|-------|
| Expected Mean (SD) | 54.4 (21.4) | | 79.7 (16.6) | |
| Sample Size | 380 | 320 | 380 | 320 |
| 95% confidence interval half width | 2.152 | 2.345 | 1.669 | 1.819 |
| Standard error (SE) | 1.098 | 1.196 | 0.852 | 0.928 |

Table 2. 95% confidence interval (CI) half-width and standard error (SE) of the expected mean assuming N=380/320 evaluable patients [19]

In all considered scenarios the relative error of the estimate (CI half-width/expected mean) is lower than 30%. The lower the sample size and the higher the standard deviation, the lower the estimate precision.

9.6 DATA MANAGEMENT

The CROs in charge of the study is [REDACTED].

The data entered into the eCRFs by investigational staff will be reviewed for completeness and accuracy and the site personnel will be instructed to data entry data into the eCRFs and to make any required corrections or additions. In order to validate the e-CRF content a qualitative pre-test will be performed, by simulating data capture during study conduction.

The Data Manager will perform the cleaning session by running post-entry checks by means of validation programs and data listings specific for the study. During this process, if clarifications are needed, the Data Manager will raise queries by means of data query forms

through the application. Designated investigator site staff is required to respond to the query and make the correction to the database.

Patients violating inclusion/exclusion criteria will not be considered for analyses. A description of reasons of violation will be provided anyway. After these actions have been completed and the database has been declared to be completed and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Medical Adviser, the Trial Statistician and the Data Manager. Only authorized and well-documented updates to the study data will be possible after database lock.

Each participating site will maintain appropriate medical and research records for this study, in compliance with GPP and regulatory and institutional requirements for the protection of confidentiality of subjects.

Patient initials or names will not be recorded in the database: patients will be associated to a unique identifier, assigned as a progressive number within each site. Due to the observational nature of the study no independent review of the data will be performed.

Data access rules, as well as data transfer to Sponsor, will be detailed in the Data Management Plan.

9.7 DATA ANALYSIS

Descriptive analysis will be means, medians, quantiles, proportions (with their respective 95% confidence intervals and SE when relevant) and contingency tables according to the nature of the variables. As a dispersion measurement the standard deviation and the interquartile range will be calculated.

Statistical analysis will be performed using the SAS software.

The statistical analysis will be done on all evaluable patients i.e. patients who enter the study without inclusion-exclusion criteria violations and with at least one TSQM-9 domain score (effectiveness, convenience and global satisfaction) calculated. Enrolled patients not evaluable for analysis will be described in terms of frequency of violations and according main socio-demographic variables (such as age and gender), clinical (such as disease severity and number of exacerbations in the 12-month before enrollment) and treatment satisfaction scores (if available) at baseline.

Patients with missing values will not be excluded from the analysis, their data will not be replaced; frequency of missing data will be given for all analyzed variables. Lost to follow up patients will be analyzed until their last available visit.

Appropriate descriptive statistics for main socio-demographic (gender, age, race, education and employment status, smoking habits) and clinical variables (medical history for COPD and not, disease severity and awareness) at baseline visit will be presented to describe the study population at inclusion. Patients at inclusion in the study will be also described in terms of ongoing pharmacological and non pharmacological treatments for COPD.

Moreover, the study population will be described in terms of number of exacerbations occurred during study period and changes in COPD medication since baseline.

The study objectives will be evaluated as below described.

Primary objective

The patients' satisfaction for medical treatment will be assessed by the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9) at each study visit (45, 46). TSQM-9 is a self-rated tool for evaluating patient satisfaction to medical therapy. It is composed by 3 domains covering efficacy, convenience and global treatment satisfaction. TSQM-9 scores will be calculated according to author's instructions and summarized at each time point on all evaluable patients. Patients lost to follow up will be considered until their last available visit.

The patients switching treatment during observation period will not be excluded from analysis and will be evaluated at each visit as above described. Few patients are expected to stop treatment during study; if any, for primary objective evaluation they will be censored at the latest available visit. Comparisons of satisfaction between different treatment/devices are not matter of this study, throughout all analysis treatments will be lumped together.

Secondary objectives

#1 To describe patient disease perception (B-IPQ), adherence to COPD treatment (MMAS4), health status (CAT) and dyspnea (MMRC) during a 12-month observation period

A description of B-IPQ (consequences, timeline, personal control, treatment control, identity, concern, emotions and illness comprehensibility), MMAS-4, CAT and MMRC scores will be provided at baseline and at follow-up visits. Scale scores will be summarized at each time point. Patients lost to follow up will be considered until their last available visit. Missing items of questionnaires/scales will be replaced if applicable according to scoring algorithm [32-38].

#2 To analyse the relation between treatment satisfaction for medical treatment and demographic/clinical parameters and PROs during a 12-month observation period

Three regression models (one for each TSQM-9 domain score) will be estimated; the dependent variable will be domain score and the independent ones will be: age and gender (at enrollment), number of exacerbations, relevant spirometry parameters (such as FEV1, FVC, FEV1 % of the predicted, RV, TLC, DLCO), level of dyspnea (MMRC score), impact of COPD on a patient's life (CAT) and treatment adherence (MMAS-4 score) collected during observational period. Because dependent variable will be collected at each study visit, repeated measures models will be estimated taking into account all available values for dependent and independent variables. Patients could be classified in mild or moderate/severe according to lung function parameters. This will allow to evaluate treatment satisfaction in different groups of patients.

The patients switching treatment during observation period will not be excluded from analysis and will be evaluated at each visit. The patients stopping treatment during study will be censored at last available visit.

#3 To describe the health care resources utilization and related cost during a 12-month observation period

The health care resources consumption will take into consideration the following events related to management of COPD and COPD exacerbations: inpatients and outpatients hospitalization (inward and day-hospital), accesses to emergency room, General Practitioner (GP) and outpatient visits, laboratory tests and examinations, pharmacological (LABA, LAMA, SABA, SAMA, ICS/LABA, steroids, antibiotics, long-Term Oxygen Therapy, etc.) and non-pharmacological therapies (pulmonary rehabilitation) occurred/administered during study period.

Medications for adverse events will be considered too.

The annual direct health care resource consumption and related cost will be provided by means of descriptive statistics of the variables mentioned above. In order to describe the health care cost from enrolment up to the end of 12-month follow-up according to the INHS point of view (26), a two steps approach will be followed: (i) first of all the resource consumed since enrolment will be calculated and then (ii) a monetary value will be assigned to the resource consumption.

(i) Health care resources consumption exclusively related to COPD, COPD exacerbations and COPD-drug-related adverse events will be computed during observational period in terms of pharmacological and non-pharmacological treatments, number of (inward and day-hospital) hospitalizations, number of emergency room accesses, number of GP visits, specialist visits, laboratory tests or examinations (spirometry, FEV1, FVC, FEV1 % of the predicted, RV, IC, TLC, DLCO).

(ii) In order to estimate the economic impact on health care sector related cost (30) of the above mentioned health services (hospital admissions, visits, treatments, examinations, spirometry) consumption, a monetary value to each event recorded will be assigned, as defined by the Italian Ministry of Health through the tariffs in force for outpatient setting (31). The cost of hospitalization will be valued according to the most recent available diagnosis-related group (DRG) tariffs (32); finally, pharmacological treatments will be costed at consumer price. All costs will be expressed in €2015. A monthly (or yearly) cost will be provided by taking into account patients according to duration of observation and parametrizing each patient to the 12-month observation period.

Descriptive statistics (mean, standard deviation, median, minimum and maximum) of the annual direct health care resource consumption and related cost will be provided.

Non-parametric bootstrap method will be applied to cost data for calculating 95% confidence intervals (22-23).

A multiple linear regression model will be performed to investigate statistical significance of INHS cost predictors (24).

#4 To assess the correlation between patients' satisfaction and resource utilization.

Correlation indexes will be calculated between treatment satisfaction domain scores of TSQM-9 and healthcare resource consumption (such as number of hospitalizations, emergency room accesses, GP visits, laboratory test. etc... during observation period) at 12-month follow-up visit. The patients switching treatment during observation period will not be excluded from analysis and will be evaluated at each visit. The patients stopping treatment during study will be censored at their last available visit.

9.8 QUALITY CONTROL

The Quality control will be managed in accordance with [REDACTED] procedures as agreed with BITSPA.

9.9 STUDY MONITORING

On site and remote monitoring will be performed by [REDACTED] who has been designated by BITSPA.

It is understood that the monitor(s) will contact and/or visit the Investigator/centre before the study start up, regularly throughout the study and after the study data collection will have been completed, and that they will be permitted to inspect the various study records: eCRFs, filled questionnaire, Investigator study file and source data (source data is any data that is recorded elsewhere to the eCRFs), provided that subject confidentiality is respected.

The purposes of these visits/phone contacts are:

- to assess the progress of the study;
- to review compliance with the study protocol;
- to discuss any emerging issue;
- to check the eCRFs for accuracy and completeness;
- to validate the contents of the eCRFs against the source documents (only by on site visits).

Prior to each on site monitoring visit, the Investigator or staff will record all data generated since the last visit on the eCRFs. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.

During each remote monitoring contact, the Investigator or staff will will be expected to be available for the phone call to answer questions and to provide any missing information.

9.10 GUIDELINES FOR EPIDEMIOLOGICAL STUDIES

The guidelines for Good Pharmacoepidemiology Practices (GPP) in non-interventional studies as well as recommendations for non-interventional study and principles of epidemiology studies will be respected [47]. This study is not in the scope of Good Clinical Practice (GCP) studies, but for several aspects it will be managed according to it.

9.11 CONFIDENTIALITY OF STUDY DOCUMENTS AND SUBJECT RECORDS

All study documents are provided by the Sponsor to the Investigator and his/her appointed staff in confidence. None of this material may be disclosed to any party not directly involved in the study without written permission from BITSPA.

The Investigator must assure that the subject's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the subject's study numbers, names and telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from BITSPA.

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Only the subject number will be recorded in the case report form. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigators will maintain a list to enable subjects' records to be identified. However, if the results of the study are published, the subject's identity will remain confidential.

Personal data - including sensitive data - collected during the execution of the activities will be processed in accordance with the local laws on data protection.

9.12 INVESTIGATOR'S FILES / RETENTION OF DOCUMENTS

The Investigator must maintain adequate and accurate records to enable the conduct of this cohort study and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) Investigator's Study File, and (2) subject clinical source documents.

The Investigator's Study File will contain the observational protocol study/amendments, EC/IRB approval with correspondence, sample informed consent, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.

Subject clinical source documents would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, pathology and special assessment reports, signed informed consent and privacy forms, consultant letters and subject screening and enrollment logs. The Investigator must keep these two categories of documents on file according to local regulations after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, BITSPA must be notified in advance.

9.13 LIMITATIONS OF THE RESEARCH METHODS

This is a non-interventional (observational) study which puts patients under observation for one year prospectively. However information, selection and/or recall bias have to be taken into account, as in all non-interventional studies.

Investigators could select patients in order to enroll those ones who most probably will be followed up or most probably correctly understand the questionnaires (selection bias). In order to limit this bias, monitoring visits could be randomly performed in sites to verify whether enrolment was performed consecutively.

The information to be captured is usually recorded in medical charts or on questionnaires filled in during visit: this also should limit recall bias of information.

As regards confounding, the primary aim of the study is to evaluate the patients' satisfaction for medical treatment irrespective of the ongoing treatment, no causality nor associations to treatments will be evaluated because of the lack of a control group. The regression models to analyze the relation between treatment satisfaction scores and demographic, clinical and PROs parameters during a 12-month observation (secondary objective #2) will provide adjusted estimates of the impact on satisfaction scores of each variable keeping constant the others included in the models.

Patients with missing values will not be excluded from the analysis, their data will not be replaced; frequency of missing data will be given for all analyzed variables. Patients with missing and not missing values in TSQM9 domain scores will be described according to main socio-demographic and clinical features.

As far as generalizability of results, the study aims to provide information on COPD patients enrolled in the study; it does not mean to be generalized to the population of Italian COPD patients, because sites are selected. However sampling is based on consecutive enrolment, in order to avoid patient selection during recruitment.

Finally, target sample size is considered to be achievable during the enrolment period on the basis of preliminary feasibility considerations.

9.14 OTHER ASPECTS

9.15 INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS

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) 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 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.

9.16 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) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from each patient according to ICH GCP and to the regulatory and legal requirements of Italy. 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 or the patient's legally accepted representative.

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 Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.16.1 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IRBs/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 at any time according to the Sponsor's Standard Operating Procedures, in order to verify whether the study is being conducted in agreement with GPP.

The Investigators and Institution must permit study-related monitoring, audits, IRBs/IECs review or regulatory inspection, providing direct access to source data/documents.

9.16.2 RECORDS

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

9.16.3 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 eCRFs 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.

For eCRFs all data must be derived from source documents

9.16.4 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. CRFs/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. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section.

9.16.5 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.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. 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.

9.16.6 COMPLETION OF STUDY

The IRB/IEC/competent authority in Italy will be notified about the end of the study (date of termination of observational study, last patient out date, number of patients observed) or early termination of the observation.

9.16.7 PROTOCOL VIOLATIONS

Not applicable

9.16.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

This study was designed and shall be implemented and reported in accordance with the Guide on Methodological Standards in Pharmacoepidemiology (Revision 3, July 2014) of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, with the ethical principles laid down in the Declaration of Helsinki and with the laws and regulations of Italy in which the research is carried out, whichever affords the greater protection of the individual.

The study will be notified to the Health Authority according to the legal requirements in Italy as unique participating country.

Subjects selection will not start before the approval of the EC/IRB and notification of the study to the Health Authority. This study does not include treatments or diagnostic examinations other than those prescribed in the ordinary clinical practice, therefore no insurance agreements are applicable.

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 subject 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.

Adverse Event of Special Interest (AESI)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within

this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs

The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the (e)CRF from signing the informed consent onwards until the end of the study for the BI product administered for the disease in scope of the study:

- all ADRs (serious and non-serious),
- all AEs with fatal outcome ,
- all pregnancies

All ADRs , 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 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 etiologies** that could explain the event (e.g. preexisting 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.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

- Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate: Enough discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject, has been enrolled into the study after having taken the BI drug taken for the disease in scope of the study, the investigator must report any drug exposure during pregnancy which occurred in a female subject or in a partner to a male subject 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 NIS 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 on the NIS AE form (or pregnancy monitoring form if applicable) from signing the informed consent onwards until the end of the study for the BI product administered for the disease in scope of the study:

| Type of Report | Timeline |
|-----------------------------------|-----------------------------|
| All SADRs | immediately within 24 hours |
| All AEs with fatal outcome | immediately within 24 hours |
| All non-serious ADRs | 7 calendar days |
| All pregnancies | 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 NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE 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 the BI drug taken for the disease 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 MAH according to local and international regulatory requirements. Also the investigator is encouraged to report all adverse event related to any drug to LHA according to local regulatory requirements

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The end of the data collection (including the follow-up period) for this observational study is expected within 2017.

The final study report should be submitted as soon as possible within 12 months of the end of data collection.

The final study report, including the statistical and clinical evaluations, shall be prepared and sent to the Advisory Board, for agreement and signature.

At the end of the study a summary of the final study report will be provided to all ECs/IRBs, to the Italian Competent Authority, only if requested, and to Investigators.

BITSPA is entitled to publish and/or present any results of this study at scientific meetings; BITSPA furthermore reserves the right to use such data for industrial purposes.

Investigators will inform the Advisory Board and BITSPA before using the results of the study for publication or presentation, and agree to provide the Sponsor with a copy of the proposed presentation. Data from individual study sites shall not be published separately before main study paper based on global data collected will be published.

12.1 OPERATIVE MANAGEMENT OF MEDICAL WRITING ASPECTS

The results of this study will be published or presented at scientific meetings. Participant Investigator agrees to submit all manuscripts or abstracts to BITSPA prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, BITSPA will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, the Study Advisory Board will be designated.

The investigator has to provide the sponsor all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials, is the sole responsibility of the sponsor.

Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Study Site Agreement, which has to be written consequently.

BITSPA also adheres to any additional standards concerning authorship required by a specific journal or congress to which the publication is submitted. The responsible

individuals at BISPA apply, at a minimum, the following criteria to determine who is named as an author on a publication:

- Substantial contributions to the concept and design, acquisition of data, or analysis and interpretation of data
- Drafting of the publication or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authorship criteria and obligations apply equally to BITSPA employees and non-employees. Each listed author must have participated in the work enough to take public responsibility for appropriate portions of the content.

Individuals contributing to the publication but not meeting authorship criteria may be appropriately acknowledged in the publication.

12.2 GHOSTWRITING AND GUEST/GHOST AUTHORSHIP

Ghostwriting, guest authorship, and ghost authorship are strictly prohibited. The contribution of a writer, which, when performed under the direction of the author(s), is considered a form of specialized, technical assistance, is acknowledged in the earliest draft in which the writer is involved.

12.3 DETERMINING ORDER OF AUTHORSHIP

Author order is determined by mutual agreement at the earliest possible time, with due consideration to overall contributions to the study, to the publication, or to scientific knowledge of the subject matter.

13. REFERENCES

13.1 PUBLISHED REFERENCES

1. Meek PM, Schwartzstein RM, Adams L, Altose MD, Breslin EH, Carrieri-Kohlman V, Gift A, Hanley MV, Harver A, Jones PW, Killian K, Knebel A, Lareau SC, Mahler DA, O'Donnell D, Steele B, Stuhlbarg M, Titler M. Dyspnea: mechanisms, assessment, and management: a consensus statement. *Am J Respir Crit Care Med* 1999;159(1):321-40
2. Stenton C. The MRC breathlessness scale. *Occup Med (Lond)* 2008;58(3):226-7
3. Jones NL. Exercise testing in pulmonary evaluation: clinical applications. *N A Engl J Med* 1975;293(13):647-50
4. Eisner MD, Blanc PD, Yelin EH, Sidney S, Katz PP, Ackerson L, Lathon P, Tolstykh I, Omachi T, Byl N, Iribarren C. COPD as a systemic disease: impact on physical functional limitations. *Am J Med* 2008;121(9):789-96
5. Kapella MC, Larson JL, Covey MK, Alex CG. Functional performance in chronic obstructive pulmonary disease declines with time. *Med Sci Sports Exerc* 2011;43(2):218-24
6. Miravittles M, Anzueto A, Legnani D, Forstmeier L, Fargel M. Patient's perception of exacerbations of COPD - the PERCEIVE study. *Respir Med* 2007;101(3):453-60
7. Williams V, Bruton A, Ellis-Hill C, McPherson K. What really matters to patients living with chronic obstructive pulmonary disease? An exploratory study. *Chronic Respir Dis* 2007;4(2):77-85
8. Hill K, Goldstein RS. Limited functional performance in chronic obstructive pulmonary disease: nature, causes and measurement. *COPD J Chronic Obstruct Pulm Dis* 2007;4(3):257-61
9. Bharmal M, Payne K, Atkinson M J, Desrosiers MP, Morisky ED and Gemmen E: Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. *Health and Quality of Life Outcomes* 2009;7:36-46
10. Baiardini I, Bousquet PJ, Brzoza Z, Canonica GW, Compalati E, Fiocchi A, Fokkens W, van Wijk RG, La Grutta S, Lombardi C, Maurer M, Pinto AM, Ridolo E, Senna GE, Terreehorst I, Bom AT, Bousquet J, Zuberbier T, Braido F; Global Allergy and Asthma European Network. Recommendations for assessing patient-reported outcomes and health-related quality of life in clinical trials on allergy: a GA(2)LEN taskforce position paper. *Allergy*. 2010;65(3):290-5
11. Weaver M, Patrick DL, Markson LE, Martin D, Frederic I, Berger M. Issues in the measurement of satisfaction with treatment. *Am J Manag Care* 1997;3(4):579-94
12. van Campen C, Sixma H, Friele RD, Kerssens JJ, Peters L. Quality of care and patient satisfaction: a review of measuring instruments. *Med Care Res Rev* 1995;52(1):109-33
13. Kravitz RL, Callahan EJ, Paterniti D, Antonius D, Dunham M, Lewis CE. Prevalence and sources of patients' unmet expectations for care. *Ann Intern Med* 1996 ;125(9):730-7

14. Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-26
15. Barbosa CD, Balp MM, Kulich K, Germain N, Rofail D. A literature review to explore the link between treatment satisfaction and adherence, compliance, and persistence. *Patient Preference and Adherence* 2012;6:39-48
16. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, Grinten CPM van der, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; Standardisation of spirometry. *Eur Respir J* 26 (2), 319 - 338 (2005)
17. Saiz A, Mora S, Blanco J; en representación de los investigadores del estudio COMPLIANCE. Therapeutic compliance of first line disease-modifying therapies in patients with multiple sclerosis. COMPLIANCE Study. *Neurologia*. 2015;30:214-222.
18. Schaarschmidt ML, Kromer C, Herr R, Schmieder A, Goerdts S, Peitsch WK. Treatment satisfaction of patients with psoriasis. *Acta Derm Venereol*. 2015 28;95:572-8.
19. Dixon, W.J., Massey, F.J. Introduction to Statistical Analysis. 4th Edition McGraw-Hill (1983)
20. Bharmal M, Payne K, Atkinson MJ, Desrosiers MP, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. *Health Qual Life Outcomes*. 2009;7:36
21. Efron B, Tibshirani RJ. An Introduction to the Bootstrap. Chapman and Hall: New York, 1993
22. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. *Statistics in Medicine* 2000;19(23):3219-36
23. Petrucci MT, Calabrese E, Levi A, Federico V, Ceccolini M, Rizzi R, Gozzetti A, Falco P, Lazzaro C, Martelli E, Boccadoro M, Lauria F, Liso V, Cavo M, Foa R. Cost of illness in patients with multiple myeloma in Italy: the CoMiM study. *Tumori* 2013; 99(4):e193-202
24. The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208
25. Brazier J, Jones N, Kind P. Testing the validity of the Euroqol and comparing it with the SF-36 Health Survey questionnaire. *Qual Life Res* 1993;2(3):169-80
26. Dolan P. Modeling valuations for EuroQol health states. *Medical Care* 1997; 35(11):1095-108
27. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727-36
28. Rabin R, Oemar M, Oppe M, Janssen B, Herdman M. on behalf of the EuroQol Group. EQ-5D-5L User Guide. Basic information on how to use the EQ-5D-5L instrument. EuroQol Group 2011. Version 1.0 Rotterdam, The Netherlands: EuroQol Group, April 2011
29. Drummond MF, Schulper MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. 3rd ed. Oxford, UK: Oxford University Press, 2005

30. Ministero della Salute. Decreto 18 ottobre 2012. Remunerazione prestazioni di assistenza ospedaliera per acuti, assistenza ospedaliera di riabilitazione e di lungodegenza post acuzie e di assistenza specialistica ambulatoriale. (13A00528). Gazzetta Ufficiale della Repubblica Italiana Serie Generale, n. 23 del 28 gennaio 2013. Allegato 3. Prestazioni di assistenza specialistica ambulatoriale
31. Conferenza Permanente per i Rapporti tra lo Stato le Regioni e le Province Autonome di Trento e Bolzano, 2014. Tariffa unica convenzionale per le prestazioni di assistenza ospedaliera regole e tariffe valide per l'anno 2013. Roma: Conferenza Permanente per i Rapporti tra lo Stato le Regioni e le Province Autonome di Trento e Bolzano, 2014, 29 maggio 2014
32. Krauskopf K, Federman AD, Kale MS, Sigel KM, Martynenko M, O'Connor R, Wolf MS, Leventhal H, Wisnivesky JP Chronic Obstructive Pulmonary Disease Illness and Medication Beliefs are Associated with Medication Adherence. COPD. 2015 Apr;12(2):151-64.
33. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2014 Update. <http://www.goldcopd.org/> (10.05.2014).
34. Pasquale MK, Sun SX, Song F, Hartnett HJ, Stemkowski SA. Impact of exacerbations on health care cost and resource utilization in chronic obstructive pulmonary disease patients with chronic bronchitis from a predominantly Medicare population. Int J Chron Obstruct Pulmon Dis 2012; 7: 757-64.
35. Minov J, Karadzinska-Bislimovska J, Vasilevska K, Stoleski S, Mijakoski D. Course of COPD Assessment Test (CAT) Scores During Bacterial Exacerbations of Chronic Obstructive Pulmonary Disease Treated in Outpatient Setting. Open Respir Med J. 2015 Mar 31;9:39-45.
36. Mahler DA, Ward J, Waterman LA, Baird JC. Longitudinal changes in patient-reported dyspnea in patients with COPD. COPD. 2012 Aug;9(5):522-7.
37. Abdullah Sayiner, Ashraf Alzaabi, Nathir M. Obeidat, Chakib Nejjari, Majed Beji, Esra Uzaslan, Salim Nafti, Javaid Ahmed Khan, Mohamed Awad Tageldin, Majdy Idrees, Nauman Rashid, Abdelkader El Hasnaoui, on behalf of the BREATHE Study Group Attitudes and beliefs about COPD: Data from the BREATHE study. Respiratory Medicine (2012) 106(S2), S60–S74
38. Junji Lin, Yunfeng Li, Haijun Tian, Michael J Goodman, Susan Gabriel, Tara Nazareth, Stuart J Turner, Stephen Arcona, and Kristijan H Kahler Costs and health care resource utilization among chronic obstructive pulmonary disease patients with newly acquired pneumonia Clinicoecon Outcomes Res. 2014; 6: 349–356
39. Ismaila A, Corriveau D, Vaillancourt J, Parsons D, Dalal A, Su Z, Sampalis JS. Impact of adherence to treatment with tiotropium and fluticasone propionate/salmeterol in chronic obstructive pulmonary diseases patients. Curr Med Res Opin. 2014 Jul;30(7):1427-36.

40. Dal Negro RW, Bonadiman L, Turco P, Tognella S. Costs of illness analysis in Italian patients with chronic obstructive pulmonary disease (COPD): an update. *ClinicoEconomics and Outcomes Research* 2015;7 153–159
41. P.W. Jones, G. Harding, P. Berry, I. Wiklund, W-H. Chen and N. Kline Leidy Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009; 34: 648–654
42. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. 1986 Jan;24(1):67-74.
43. Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: Final response. *J Clin Epidemio* 2011; 64:258-263.
44. Morisky DE, Malotte CK, Choi P, et al. A Patient Education Program to Improve Adherence Rate with Antituberculosis Drug Regimens. *Health Education Quarterly* 1990; 17:253-268.
45. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, Rowland CR: Validation of a general measure of treatment satisfaction the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes* 2004, 2:12
46. Atkinson MJ, Kumar R, Cappelleri JC, Hass SL: Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. *Value Health*. 2005 Nov-Dec;8 Suppl 1:S9-S24.
47. Broadbent E et al. “The Brief Illness Perception Questionnaire”. *Journal of Psychosomatic Research*. 2006; 60: 631– 637
48. Osservatorio Nazionale sull’impiego dei medicinali. L’uso dei farmaci in Italia – Rapporto Nazionale 2013

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

List of Advisory Board members

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

A copy of the ENCePP Checklist for Study protocols available at website: encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1:

“Study start” means “Start of data collection”

“Study progress” means “Progress report(s)”

“Study completion” means “End of data collection”

“Reporting” means “Final report of the study results”

See attached file

ANNEX 3. ADDITIONAL INFORMATION

None.