TITLE PAGE

Document Number:	c06524595-04
BI Study Number:	1237.45
BI Investigational Product(s):	Spiolto® Respimat®
Title:	Assessment of physical functioning and handling of Spiolto® Respimat® in patients with chronic obstructive pulmonary disease (COPD) requiring long-acting dual bronchodilation in routine clinical practice
Protocol version identifier:	3.0
Date of last version of protocol:	21 April 2017
PASS:	No
EU PAS register number:	EUPAS12750
Active substance:	R03AL06 Tiotropium bromide + Olodaterol
Medicinal product:	Spiolto® Respimat® 2.5 microgram/2.5 microgram, inhalation solution; tiotropium/olodaterol
Product reference:	NL/H/3157/001/DC
Procedure number:	n.a.
Marketing authorisation holder(s):	Market Authorisation Holder: Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein Study initiator:
Joint PASS:	No
Research question and objectives:	The objective of this NIS is to measure changes in physical functioning – a surrogate for physical activity and exercise capacity – in COPD patients on treatment with Spiolto® Respimat® in routine daily treatment after approximately 6

	weeks. A secondary objective is to evaluate the patient's general condition (physician's evaluation) from Visit 1 (baseline visit at the start of the study) to Visit 2 (final visit at the end of the study, approx. 6 weeks after Visit 1), as well as patient satisfaction with Spiolto® Respimat® at Visit 2.
Country(-ies) of study:	6 countries: Belgium, Denmark, Sweden, The Netherlands, Luxembourg, Portugal
Author:	(Medical Team Respiratory MIDI) Mobile: (Trial Clinical Monitor) Mobile:
EU PAS Register Number	EUPAS12750
Date:	21 April 2017

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BI	Boehringer Ingelheim
CA	Competent Authority
CI	Confidence Interval
CML	Local Clinical Monitor
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
DMP	Data Management Plan
EU	European Union
FDC	Fix Dose Combination
FEV1	Forced expiratory volume in one second
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICH	International Conference on Harmonisation
ICS	Inhalative Corticosteroides
IEC	Independent Ethics Committee
ISF	Investigator Site File
LABA	Long-acting $beta_2$ adrenoceptor agonist
LAMA	Long-acting muscarinic antagonist
MedDRA	Medical Dictionary for Drug Regulatory Activities
mMRC	Modified Medical Research Council
NIS	Non-Interventional Study
PF-10	Patient questionnaire
PGE	Physician's Global Evaluation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	36-Item Short Form Health Survey
SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

Therapeutic Area Respiratory Medicine (TA)	
Team Member Medical Affairs (TM MA)	
Team Member Epidemiology (TM Epi)	
Global Epidemiology (GEpi)	
Therapeutic Area Risk Management (TA RM), and Pharmacovigilance Working Group (PVWG)	
GPV Study Coordination	
Trial Statistician (TSTAT)	
Trial Data Manager (TDM)	
Trial Programming	
Medical Team Respiratory	
Trial Clinical Monitor (TCM)	
Coordinating Investigator (CI)	not applicable
CRO –	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 02 Mar 2016	**Study number:** 1237.45	**Version/Revision:** 3.0	**Version/Revision date:** 21 Apr 2017
Title of study:	Assessment of physical functioning and handling of Spiolto® Respimat® in patients with chronic obstructive pulmonary disease (COPD) requiring long-acting dual bronchodilation in routine clinical practice.		
Rationale and background:	Reduced physical activity resulting in deconditioning and restricted physical functioning is a common problem of patients with moderate to severe COPD. Clinical studies investigating treatment with Spiolto® Respimat® and its single components have shown significant improvements in exercise capacity in patients with COPD. Real-world data on the effects of a fixed-dose combination (LABA+LAMA) therapy with tiotropium and olodaterol administered in a single device, in COPD patients who need treatment with two long-acting bronchodilators, is not available.		
Research question and objectives:	The primary objective of this NIS is to measure changes in physical functioning – a surrogate for physical activity and exercise capacity – in COPD patients on treatment with Spiolto® Respimat® in routine daily treatment after approximately 6 weeks. A secondary objective is to evaluate the patient's general condition (physician's evaluation) from Visit 1 (baseline visit at the start of the study) to Visit 2 (final visit at the end of the study, approx. 6 weeks after Visit 1), as well as patient satisfaction with Spiolto® Respimat® at Visit 2.		
Study design:	Open-label observational study: 6 countries, including COPD patients receiving treatment with Spiolto® Respimat® for approximately 6 weeks, which is the average time between two medical consultations.		
Population:	COPD patients requiring a fixed combination therapy of two long-acting bronchodilators (LAMA + LABA) according to approved SmPC and GOLD guidelines.		
Variables:	- Patient demographics (age, gender, height & weight) - Concomitant diseases / Comorbidities - Concomitant medication - General condition of patient based on Physician's Global		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 02 Mar 2016	**Study number:** 1237.45	**Version/Revision:** 3.0	**Version/Revision date:** 21 Apr 2017
	Evaluation (PGE) - Smoking history - Exacerbations - Breathlessness based on mMRC score - Physical Functioning based on PF-10 scores - Patient satisfaction with Spiolto® Respimat® - Safety; ADR (serious and non-serious), fatal AEs, pregnancies - GOLD spirometric classifications (1, 2, 3, 4) - GOLD patient groups (A, B, C, D)		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 02 Mar 2016	**Study number:** 1237.45	**Version/Revision:** 3.0	**Version/Revision date:** 21 Apr 2017
Data sources:	To be completed by the physician: - Patient demographics - Patient medical files - Physician's Global Evaluation (PGE) at Visit 1 and Visit 2 To be completed by the patient at Visit 1: - mMRC breathlessness scale To be completed by the patient at Visit 1 and at Visit 2: - Physical Functioning Questionnaire (PF-10) To be completed by the patient at Visit 2 only: - Patient satisfaction survey		
Study size:	1200 patients, 225 sites; 6 countries: Belgium, Denmark, Sweden, The Netherlands, Luxembourg, Portugal		
Data analysis:	**Primary outcome:** "therapeutic success" at Visit 2 (= 10-point increase in the PF-10 score between Visit 1 and Visit 2). **Secondary outcomes:** - Changes in the PF-10 score from Visit 1 to Visit 2 - General condition of the patient, evaluated by the physician (PGE score) at Visit 1 and Visit 2. - Patient satisfaction with Spiolto® Respimat® at Visit 2.		
Milestones:	Start of data collection End of data collection Final report of study results	September 2016 March 2018 June 2018	

5. AMENDMENTS AND UPDATES

Protocol v3.0, Amendment 2				
Number	**Date**	**Section of study protocol**	**Amendment or update**	**Reason**
1	21 Apr 2017	Front Page, p. 2	Changing countries of the study	Deleting Norway, Adding Portugal
2	21 Apr 2017	Front Page, p. 2	Adding protocol author	New Medical Team Leader Respiratory MIDI
3	21 Apr 2017	Front Page, p. 2	Adding protocol author	New TCM
4	21 Apr 2017	Paragraph 3 Responsible parties, p. 6	Changing Therapeutic Area Head Risk Management (TAH RM), and Pharmacovigilance Working Group (PVWG) chairperson	New Therapeutic Area Head Risk Management (TAH RM), and Pharmacovigilance Working Group (PVWG) chairperson
5	21 Apr 2017	Paragraph 3 Responsible parties, p. 6	Changing Trial Data Manager	New Trial Data Manager
6	21 Apr 2017	Paragraph 3 Responsible parties, p. 6	Changing Trial Programming	New Trial Programmer
7	21 Apr 2017	Paragraph 3 Responsible parties, p. 6	Changing Medical Team Leader Respiratory	New Medical Team Leader Respiratory
8	21 Apr 2017	Paragraph 3 Responsible parties, p. 6	Changing TCM name	New TCM
9	21 Apr 2017	Paragraph 4 Abstract, p. 9	Changing study size	Changing number of sites from 250 to 225
10	21 Apr 2017	Paragraph 4	Changing study	Deleting Norway,

		Abstract, p. 9	size	Adding Portugal
11	21 Apr 2017	Paragraph 4 Abstract, p. 9	Changing Milestones	Updated date of start of data collection
12	21 Apr 2017	Paragraph 4 Abstract, p. 9	Changing Milestones	Updated date of end of data collection
13	21 Apr 2017	Paragraph 4 Abstract, p. 9	Changing Milestones	Updated date of Final report of study results
14	21 Apr 2017	Paragraph 6, p. 12	Changing Milestones	Updated date of end of data collection
15	21 Apr 2017	Paragraph 6, p. 12	Changing Milestones	Updated date of Final report of study results
16	21 Apr 2017	Paragraph 9 Research Methods, p. 17 and p. 18	Changing setting (9.2) and Selection of Patient Population (9.2.1.)	Changing number of sites from 250 to 225
17	21 Apr 2017	Paragraph 9 Research Methods, p. 17 and p. 18	Changing setting (9.2) and Selection of Patient Population (9.2.1.)	Deleting Norway, Adding Portugal
18	21 Apr 2017	Paragraph 9 Research Methods, p. 18	Change in exclusion criteria (9.2.3.)	Change in exclusion criterion n°2: “previous 6 weeks” instead of “previous 6 months”
19	21 Apr 2017	Paragraph 9 Research Methods, p. 18	Adding note in exclusion criteria (9.2.3.)	Adding note to clarify exclusion criterion n° 2

6. MILESTONES

Milestone	Planned Date
Start of data collection	September 2016
End of data collection	March 2018
Final report of study results:	June 2018

7. RATIONALE AND BACKGROUND

7.1 MEDICAL BACKGROUND

COPD is defined as a preventable and treatable disease of the airways, with significant systemic consequences. Inactivity is believed to be crucial to the development of the extrapulmonary effects of the disease like skeletal muscle weakness, osteoporosis and cardiovascular disease. Recent data suggest that patients suffering from COPD with low levels of physical activity have increased risk for hospital admission and have significantly enhanced mortality. Epidemiological data suggest that this may directly or indirectly lead to more rapid decline in lung function [R13-3633].

Physical activity is reduced early in the disease progression, as of GOLD Stage 2 [R13-3633]. More recent evidence from large placebo controlled clinical trials indicates that COPD patients are experiencing a steeper absolute decline in lung function with GOLD 2 airflow limitation than with GOLD 3 and 4 [R15-5015]. All these observations suggest the importance of early optimal treatment of the disease.

Long-acting bronchodilators, such as long-acting muscarinic antagonists (LAMAs), are the cornerstone of maintenance therapy for patients with moderate to very severe chronic obstructive pulmonary disease (COPD) whose symptoms are not adequately controlled by short-acting bronchodilators alone [P13-05794, P14-01052].

An option recommended by GOLD guideline for patients not adequately controlled on a single long-acting bronchodilator is to combine a LAMA with a long-acting β2-agonist (LABA) [P14-01052].This has prompted the development of combining LAMA+LABA as fixed-dose combinations [P13-05794]. The rationale for combining bronchodilators with different mechanisms is based on the notion of additive relaxation of airway smooth muscle by direct inhibition of cholinergic activity and functional antagonism of bronchoconstriction through β2-adrenergic pathways, with the expectation of an increase in the degree of bronchodilation for equivalent or lesser side effects. Several recent studies have provided evidence in support of this increased bronchodilatory effect when LABAs are added to LAMAs.

When long acting beta-agonists (LABA) and long acting muscarinic antagonists (LAMA) with similar or equivalent posologies are combined, the opportunity exists for offering a simpler and more convenient administration regimen with the development of fixed combinations within the same inhaler device. Fixed-dose combinations of a short-acting β2–agonist (SABA) and a short-acting anticholinergic (SAMA) have been developed and have been shown to be safe, efficacious and convenient for the patient (e.g., Berodual®: Fenoterolhydrobromid + Ipratropiumbromid, Combivent®: salbutamol + ipratropium bromide; [P94-1346]). Olodaterol is a highly selective and nearly full β2 agonist [P10-07776, P11-07720] that provides 24-h bronchodilation in patients with COPD [P13-11467, P13-14112, P13-11346, P13-11345]. Olodaterol is also associated with symptomatic benefit [P13-11341] and enhanced exercise capacity [P13-14109].

The complementary modes of action of tiotropium and olodaterol have previously been demonstrated in animal models, phase II clinical trials and during the Phase IIIa programs [P10-09337, P14-12073, P13-02357].

In the Phase III programs the additional benefits of the tiotropium + olodaterol fixed-dose combination (FDC) over its mono-components has been assessed on lung function, quality of life (St. George's Respiratory Questionnaire -SGRQ), dyspnea (Transition Dyspnea Index-TDI) and exercise endurance time. Another clinically important potential benefit of the tiotropium + olodaterol FDC over the mono components is the impact on exacerbations of COPD.

7.2 DRUG PROFILE

Tiotropium + olodaterol FDC is an aqueous solution of tiotropium and olodaterol contained in a cartridge. It is administered by using the Respimat® inhaler. One cartridge is used per inhaler, which is inserted into the device prior to first use. In pivotal clinical trials and for the intended marketed product, the clinical dose consists of two puffs once daily. The Respimat® inhaler uses mechanical energy to create a soft mist which is released over a period of approximately 1.5 seconds.

Tiotropium + olodaterol FDC was shown to be safe and well tolerated over 1 year in a moderate to very severe COPD population. The overall incidences of adverse events (AEs), serious adverse event (SAEs), fatal AEs, frequencies for cardiac events and major adverse cardiovascular event in the tiotropium + olodaterol FDC treatment group were similar to the mono-components. The nature and frequency of AEs in general was consistent with the disease under study. There were no results in the clinical development program suggesting the need for absolute contraindications for the combination product [P15-03349].

In conclusion, the clinical trials conducted to date have shown tiotropium + olodaterol FDC to be a safe, well tolerated and efficacious combination therapy according to treatment guidelines in a moderate to very severe COPD patient population [P15-04531, P15-03349]. The observed incremental bronchodilator response for the combination compared to the individual components translated into benefits that were meaningful to the patient, with improvements in several patient centered outcomes. For further information please refer to the SmPC of Spiolto® Respimat®.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RATIONALE FOR PERFORMING THE STUDY

The contribution of physical inactivity to disability in COPD is difficult to distinguish from disease progression; however, it is clear that physical activity is significantly lower in patients with COPD than in healthy controls [R13-3633].

COPD prevents patients from carrying out daily activities due to exercise intolerance, which is often attributed to limited pulmonary ventilation. Physical inactivity may be related to avoidance of exertion as a result of fear of dyspnea. Furthermore, physical inactivity has been associated with skeletal muscle weakness and exercise intolerance [R15-4559, R15-4561].

The loss of physical activity in COPD is also associated with increased mortality. Data from a study of 2386 patients with COPD demonstrated that, following adjustment for relevant confounders, subjects who reported low, moderate or high physical activity had a significantly lower risk of all-cause mortality than those with very low physical activity ($p = 0.001$) [R15-4564]. Clinical studies of both Spiriva® [P13-04267, P05-09483, P13-14109] and Striverdi® Respimat® in COPD patients have demonstrated significant improvement in exercise capacity [P13-14109].
The benefits of tiotropium + olodaterol FDC have been studied in controlled Phase III programs on exercise endurance, however, data regarding physical activity when treated with Spiolto® Respimat® is not available from a real world setting.

8.2 STUDY OBJECTIVES

The primary objective of the study is to measure changes in physical functioning - serving as a surrogate for physical activity and exercise capacity - in COPD patients being treated with Spiolto® Respimat® after approximately 6 weeks in routine clinical practice.

The secondary objectives are to evaluate the patient's general condition (physician's evaluation) at Visit 1 (baseline visit at the start of the study) and at Visit 2 (final visit at the end of the study, approx. 6 weeks after Visit 1), as well as patient satisfaction with Spiolto® Respimat® at Visit 2.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a self-controlled study design enrolling consented COPD patients who will be treated with Spiolto® Respimat® according to the approved SmPC.

Patients will be enrolled consecutively and will be followed over an observational period of approx. 6 weeks. Data as listed in Table 9.1:1 will be collected.

Table 9.1:1: Visit flow chart and data collection parameters

Parameter	**Visit 1; baseline visit**	**Visit 2; approx. 6 weeks after baseline visit**
Informed Consent	X	
Inclusion / Exclusion Criteria	X	
Patient demographics (age, gender, height, and weight)	X	
Smoking history	X	X
Start of COPD	X	
Number of exacerbations in the last 12 months	X	
Number of exacerbations leading to hospitalization in the last 12 months	X	
Past COPD therapies (6 months before Visit 1)	X	
COPD related and other relevant concomitant medication	X	X
Concomitant diseases / Comorbidities	X	X
Respimat® training (yes/no)	X	
COPD severity based on GOLD assessment[1]	X	
mMRC breathlessness scale, completed by the patient	X	
Physical functioning (PF-10) questionnaire, completed by patient	X	X
General condition of patient evaluated by Physician's Global Evaluation (PGE)	X	X
Adverse Drug Reactions (serious and non-serious), fatal AE, pregnancy	X	X
Patient satisfaction with Spiolto® Respimat®, survey completed by the patient		X
Rational for Spiolto® Respimat® treatment discontinuation (if applicable)		X
Continuation or discontinuation of treatment with Spiolto® Respimat® after the study (yes/no)		X

[1] GOLD patient group (A, B, C or D) will be automatically calculated within the eCRF based on available exacerbation history, mMRC, and GOLD spirometric classification of airflow limitation based on post-bronchodilator FEV_1 if available.

Baseline characteristics of patients being eligible and who gave Informed Consent, but were not treated in the study will also be collected.

9.1.1 Outcomes

Primary outcome:

The primary outcome is to measure "Therapeutic success" (as a 10-point increase of PF-10) between Visit 1 and Visit 2 using a physical functioning questionnaire, which is a sub-domain of the SF-36 patient questionnaire. The PF-10 sub-domain consists of 10 questions evaluating the extent of experienced restrictions while conducting usual activities. Each question of the PF-10 can be answered with "yes, limited a lot", "yes, limited a little", or "No, not limited at all", with a score of 1, 2, or 3. The scores over the 10 questions will be summed, resulting in a value between 10 (a patient answering all questions with "yes, limited a lot") and 30 (a patient answering all questions with "No, not limited at all"). The final sum of the individual scores will be standardized to a range of 0 to 100 using the following formula: 100*(sum-10)/20.

Secondary outcomes:

- Changes in the PF-10 score from Visit 1 to Visit 2
- General condition of the patient, evaluated by the physician (PGE score) at Visit 1 and Visit 2.
- Patient satisfaction with Spiolto® Respimat® at Visit 2.

9.2 SETTING

It is planned that data of approximately 1200 patients from approximately 225 sites in 6 countries will be collected. Site selection will be performed to reflect routine COPD care in the participating countries to secure representativeness of the COPD population. The following countries will participate in this non-interventional study: Belgium, Denmark, Sweden, The Netherlands, Luxembourg and Portugal.

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 irrespective of whether they have been treated or not.

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

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study, or any other administrative reasons, i.e. lack of recruitment
3. Violation of the protocol, the contract, or applicable laws and regulations for non-interventional studies, which could disturb the appropriate conduct of the NIS

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

9.2.1 Selection of Patient Population

1200 patients with chronic obstructive pulmonary disease (COPD) in whom combination treatment with long-acting bronchodilators is indicated in accordance with the guidelines are to be observed in approx. 225 sites (hospital and non-hospital pulmonary medicine physicians and general practitioners) as part of this NIS. In the six participating countries (Belgium, Denmark, Sweden, The Netherlands, Luxembourg and Portugal), sites in urban as well as rural areas will be included. The nationwide distribution of the participating sites in the six countries and the number of patients enrolled are intended to ensure that the data collected are representative.

Possible contraindications are to be checked prior to treatment with Spiolto® Respimat®. See also the latest Summaries of Product Characteristics on Spiolto® Respimat®.

Every physician is to enrol the first consecutive patients he/she chooses to treat with Spiolto® Respimat®. The inclusion of four to six patients is planned per site.
The decision to treat will be taken independently of participation in this NIS and will be made before participation is considered.

9.2.2 Inclusion criteria

Patients can be included if all of the following criteria are met:

1. Written informed consent prior to participation
2. Female and male patients ≥ 40 years of age
3. Patients diagnosed with COPD and requiring long-acting dual bronchodilation (LAMA + LABA) treatment according to approved Spiolto® Respimat® SmPC and COPD GOLD guideline recommendation

9.2.3 Exclusion criteria

1. Patients with contraindications according to Spiolto® Respimat® SmPC
2. Patients who have been treated with a LABA/LAMA combination (free and fixed dose) in the previous 6 weeks

   Note:
   - Patients previously treated with LABA or LAMA (with or without ICS) are eligible to be included in the study.
   - Patients previously treated with LABA+LAMA or LABA+LAMA+ICS cannot be included in the study, if they received this treatment in the last 6 weeks.
3. Patients continuing LABA-iCS treatment should not be additionally treated with Spiolto® Respimat® in order to avoid a double dosing of long-acting beta-agonists
4. Patients for whom further follow-up is not possible at the enrolling site during the planned study period of approx. 6 weeks
5. Pregnancy and lactation
6. Patients currently listed for lung transplantation
7. Current participation in any clinical trial or any other non-interventional study of a drug or device

9.3 VARIABLES

During the observational period, the following data will be collected in an eCRF:

- Patient demographics (age, gender, height & weight)
- Concomitant diseases / Comorbidities such as cardiovascular disease, diabetes mellitus, musculoskeletal impairment, renal diseases, liver diseases, osteoporosis, gastroesophageal reflux (GERD), or lung cancer
- COPD related and other relevant concomitant medication such as beta-blockers, beta-agonists, corticosteroids, or proton pump inhibitors
- General condition of patient based on Physician's Global Evaluation (PGE) to assess the general condition of the patient at the beginning and at the end of the study
- Smoking status (current smoker, former smoker, and never smoker) and pack-years
- Reported exacerbations based on medical history in the last 12 months and exacerbations leading to hospitalization in the last 12 months
- Assessment of the severity of breathlessness based on the Modified Medical Research Council Questionnaire (mMRC score)
- Physical Functioning based on PF-10 scores
- Patient satisfaction with Spiolto® Respimat® to assess the overall satisfaction with Spiolto® Respimat® as well as specific inhalation from the device and device handling
- Safety Reporting; Adverse Drug Reactions (serious and non-serious), fatal AEs, pregnancies at the beginning and at the end of the study
- GOLD spirometric classifications (1, 2, 3, 4), based on GOLD guidelines
- GOLD patient groups (A, B, C, D), based on GOLD guidelines

The PF-10 is a sub-domain of the SF-36 and consists of 10 questions evaluating the extent of experienced restrictions while conducting usual activities. Each question of the PF-10 can be answered with "yes, limited a lot", "yes, limited a little", or "No, not limited at all", with a score of 1, 2, or 3. The scores over the 10 questions will be summed, resulting in a value between 10 (a patient answering all questions with "yes, limited a lot") and 30 (a patient answering all questions with "No, not limited at all"). The final sum of the individual scores will be standardized to a range of 0 to 100 using the following formula: 100(sum-10)/20.

9.4 DATA SOURCES

Patient files (paper and/or electronically) of COPD patients as documented by the treating physician in his/her daily practice will be used as data source.

All participating physicians will be obliged to make a note of the patient's participation in the NIS in the patient‘s original documents.

In the event of possible queries, the participating physician must be able to identify the patient observed.

Medical information on the patient must be communicated and analysed only using the patient number.
As the physical exercise capacity of the COPD patients cannot be measured directly as part of an NIS, the evaluation of general condition by the physician and an extract from the SF-36 quality-of-life questionnaire relating to physical functioning (PF-10) will be documented as surrogate parameters.

The treating physician will use the Physician's Global Evaluation (PGE) to evaluate the general condition of the patient on an 8-point ordinal scale from 1 (very poor) to 8 (excellent). PGE will be completed before and approx. 6 weeks after treatment initiation.

The modified Medical Research Council (mMRC) scale will be used to assess the breathlessness state of the patient before the treatment. The mMRC stage (0 to 4) collected from the patient, as well as the exacerbation history and the post-bronchodilator FEV_1, will be used to automatically calculate the GOLD patient group (A, B, C, or D) in the eCRF.

The physical functioning (PF-10) questionnaire is a subscale of the validated 36-Item Short Form Health Survey and contains 10 questions about everyday physical activity and functioning. Patients will be asked to complete the PF-10, in order to evaluate their physical functioning before and after treatment with Spiolto® Respimat®.

A patient satisfaction survey will also be completed at Visit 2, using a 7-point ordinal scale with divisions from very dissatisfied to very satisfied.

9.5 STUDY SIZE

In a previous study, 205.426 with over 1000 patients treated with Spiriva® Respimat®, therapeutic success (i.e., 10-point increase in the PF-10 score between Visit 1 and Visit 2) was achieved in 61% of the patients.

However, in the present study a lower therapeutic success rate is expected as patients may be already on maintenance treatment at baseline. Assuming a 50% therapeutic success rate and a sample size of 1116 patients, the 95% confidence interval for the therapeutic success rate would be between 47.1% (lower limit) and 52.9% (upper limit).

To account for a 7% drop-out rate, the sample size becomes 1200 patients.

9.6 DATA MANAGEMENT

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. The electronic Case Report Forms (eCRFs) will include programmable edits to obtain immediate feedback if data are missing (also negative answers, unknown), out of range, illogical or potentially erroneous. These rules may encompass simple checks such as range validation or presence/absence of data. Concurrent manual data review may be performed based on parameters dictated by the DMP. Ad hoc queries to the sites may be generated and followed up for resolution. A source data quality audit may be initiated to ensure that the data in the database is accurate. Source data verification (SDV) will be performed at sites identified by a risk-based approach as needed.

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

9.7.1 Statistical design – Model

Details will be described in the statistical epidemiological analysis plan (SEAP).

9.7.2 Null and alternative hypotheses

No formal hypothesis testing will be performed since this is a self-controlled study.

9.7.3 Planned analyses

All patients who have received at least one dose of Spiolto® Respimat® will be included in the analyses; this is the treated set. All analyses will be performed on the treated set (as-treated analysis). If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis. For example, if a patient is missing the PF-10 score at Visit 1 and/or Visit 2, that patient will be excluded from the analyses for the primary endpoint of therapeutic success and the secondary endpoint of change in PF-10 from Visit 1 to Visit 2.

The assessment will be carried out using SAS® software. The statistical characteristics presented in the end-of-text tables will be N / mean / SD / min / median / max for continuous variables. Tabulations of relative and absolute frequencies will be presented for categorical variables. Incidence rates and 95% CI will be given when appropriate.

The analyses will relate to the following data:

- Patient demographics (age, gender, height, and weight);
- Comorbidities (main diagnosis and concurrent diagnosis according to MedDRA, version valid as at the time of database closure);
- COPD related and other concomitant medication (according to the WHO classification, version valid at the time of database closure)
- History of smoking
- Exacerbations
- Breathlessness based on mMRC score at Visit 1
- Physical Functioning based on PF-10 scores (therapeutic success at Visit 2); primary outcome
- Changes from Visit 1 to Visit 2 in the PF-10 score; secondary outcome
- Patient satisfaction with Spiolto® Respimat® at Visit 2 only; secondary outcome
- General condition of the patient: evaluated by the physician (Physician´s Global Evaluation (PGE)); secondary outcome
- Adverse Drug Reactions (ADR & SADR), fatal AEs, pregnancies
- GOLD spirometric classification (1,2, 3, 4)
- GOLD patient groups (A, B, C, D)

- Details of treatment with inhaled respiratory agents before the study
- Details of treatment with respiratory agents during the study
- Reasons for ending treatment during the observation period
- Details of treatment continuation / discontinuation

Main analysis

For the primary outcome, the proportion of patients with therapeutic success will be presented together with the 95% confidence interval.

Further analyses

The patient's general condition (PGE) at Visit 1 and Visit 2, patient satisfaction at Visit 2 are categorical variables so they will be analysed as tabulations of frequencies. Change from Visit 1 to Visit 2 in the PF-10 score is a continuous outcome so it will be analysed with N / mean / SD / min / median / max.

The safety data will be reported according to local requirements. As similar studies will also be performed in other European countries, data pooling might be considered at the end.

9.7.4 Handling of missing data

If less than half of the PF-10 questions are missing for a patient, the missing values will be replaced with the mean of the other values, then the PF-10 score will be calculated. If half or more than half of the PF-10 questions are missing, no score will be calculated and the PF-10 score will be marked as missing. No other missing data will be imputed. Every effort will be made to collect complete data at the specified time points.

Any removal from the analysis will be documented, stating the site and patient number as well as the reason for removal.

9.8 QUALITY CONTROL

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

Validity of data entry thus is ensured by integrated validation checks performed by the system, indicating missing or implausible entries to the document list or investigator. All corrections will be visible from the systems audit trail.

No regular source data verification is planned in this study. However, in case of decreasing compliance (i.e. of missing data, data discrepancies, protocol violations, etc.) a for-cause audit or risk-based monitoring visit will be performed.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The intention of this NIS is to collect new data on the physical functioning and exercise capacity of COPD patients on treatment with Spiolto® Respimat® in a real world setting.

A NIS is the most suitable instrument for obtaining information about the use of medicines in everyday therapeutic practice and thus for investigating prospectively questions in everyday therapeutic practice.

Consecutive enrolment will be employed to minimize selection bias. The entry criteria are non-restrictive which will permit the enrolment of a broad patient population. The choice of treatment is at the discretion of the investigator.

Selection bias could occur at the site level and the patient level. To minimize the site level selection bias, the goal is to have participating centers that have access to all available treatment options which are approved for use in that country for the targeted COPD patients. To minimize selection bias at the patient level, consecutive enrolment is performed. Information bias will be minimized by the use of standard eCRF, questionnaire and physicians' training on the study protocol.

An additional limitation is that the physical functioning questionnaire (PF-10) is assessing 10 items of the full 36-Item Short Form Health Survey (SF-36).

The 7-item satisfaction scale, which is to be completed by the patient in order to measure satisfaction with Spiolto® Respimat® use, is a self-designed Boehringer-Ingelheim scale, without a public source or validation status.

9.10 OTHER ASPECTS

9.10.1 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, and as close as possible to the standards of the International Conference of Harmonisation (ICH) Tripartite Guideline for Good Clinical Practice (GCP), Guidelines for Good Epidemiological Practice (GEP) [R10-4560], Good Pharmacoepidemiology Practice (GPP) [R09-0182] and relevant BI Standard Operating Procedures (SOPs).

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

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

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.

Insurance Cover: The requirements for insurance depend on local law and legislations in the participating country. If required, the terms and conditions of the insurance cover are made available to the investigator and the patients, and the documentation must be archived in the Investigator Site File (ISF).

9.10.1.1 Study Approval, Patient Information, and Informed Consent

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective 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.

The NIS will be reviewed by the submitted to the competent Ethics Committee before it starts, as will any amendments to the observational plan. A copy of the opinion can be found in the appropriate section of the clinical trial master file.

In addition, every participating physician is to be advised by his/her ethics committee in accordance with the rules of professional conduct.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative). 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 authorized monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IEC members, and by inspectors from regulatory authorities.

The observing physician will keep the original documents in accordance with the legal storage period.

9.10.1.2 Data Quality Assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by 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.

9.10.1.3 Records

Case Report Forms (eCRFs) for individual patients will be provided by the sponsor via remote data capture. All of the clinical data and site/investigator characteristics will be captured via a web-based Electronic Data Capturing system. The site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained.

Patients must not be identified on the eCRF by name. Appropriately coded identification (i.e. Patient numbers) must be used.

All patient questionnaires will be paper-based and will be left at the site upon completion by the patient.

9.10.1.3.1 Source Documents

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

Data entered in the 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; also current medical records must be available.

For the eCRF, the following data must be derived from source documents:

- Patient demographics (age, gender, height, and weight);
- History of smoking
- Reported exacerbations
- Past COPD therapies (6 months before visit 1)
- Respimat® training (Yes/No)
- GOLD spirometric classification (1,2, 3, 4)
- GOLD patient groups (A, B, C, D)
- Concomitant diseases / Comorbidities
- Concomitant COPD and other relevant medication
- Breathlessness based on mMRC score
- Physical Functioning (PF-10) Questionnaire
- Patient Satisfaction Questionnaire
- Adverse Drug Reactions (ADR & SADR), fatal AEs, pregnancies
- Rational for Spiolto® Respimat® treatment discontinuation (if applicable)
- Details of treatment continuation / discontinuation

9.10.1.3.2 Direct Access to Source Data and Documents

The investigator / institution will permit study-related monitoring, audits, IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities. The Clinical Research Associate (CRA) / on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in section 9.10.1.3.1.

9.10.1.4 Statement of Confidentiality

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

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

9.10.1.5 Completion of Study

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient/patient out, unless specified differently in section 6 of the observational plan) or early termination of the trial.

9.10.1.6 Protocol Violations

There are no protocol waivers. All protocol violations must be reported to the sponsor immediately.

10. PROTECTION OF HUMAN SUBJECTS

Please refer to section 9.10.1

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 unfavorable 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 drug reaction

An adverse drug reaction (ADR) 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 drug 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 judgment 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 authorisation. 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 eCRF from signing the informed consent onwards until the end of the study:

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

Note: For all patients on these data must be recorded on the AE pages in the eCRF. The separate NIS (S)AE form must be used only when eCRF system is unavailable and must be forwarded to the local Pharmacovigilance fax as indicated in the form.*

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 this study. Once a subject has been enrolled into the study with Spiolto® Respimat®, 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 (by fax) to the local Pharmacovigilance point of contact for each country within respective timelines.

Expedited Reporting of ADRs / Fatal AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator on the NIS (S)AE Form from signing the informed consent onwards until the end of the study:

Table 11.2:1 Reporting types and timelines

Type of Report*	Timeline
All **SADRs** associated with Spiolto® Respimat®	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Spiolto® Respimat®	immediately within 24 hours
All **non-serious ADRs** associated with Spiolto® Respimat®	7 calendar days
All **pregnancy monitoring** forms associated with Spiolto® Respimat®	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/email the NIS (S)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 (S)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 Spiolto® Respimat® according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results of this non-interventional study will be disclosed on encepp.eu and clinicaltrials.gov and a study specific publication plan will be developed to describe planned publications.

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13.2 UNPUBLISHED REFERENCES

n.a.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

The stand-alone documents for this non-interventional study are:

- Informed Consent Form
- Physicians' Global Evaluation (PGE)
- PF-10 Questionnaire based on SF-36
- Breathlessness Scale (mMRC)
- Patient Satisfaction Survey
- Statistical Epidemiological Analysis Plan (SEAP)
- Data Management Plan (DMP)
- Pregnancy Monitoring Form
- Serious Adverse Event Report in Non-Interventional Studies (NIS (S)AE Form)
- Publication Plan

All of the above documents will be archived in the Trial Master File in its original English master version.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Physical Functioning Questionnaire (PF-10) based on the 36-Item Short Form Survey.

Please circle one number on each line.		Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
1.	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
2.	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
3.	Lifting or carrying groceries	[1]	[2]	[3]
4.	Climbing **several** flights of stairs	[1]	[2]	[3]
5.	Climbing **one** flight of stairs	[1]	[2]	[3]
6.	Bending, kneeling, or stooping	[1]	[2]	[3]
7.	Walking **more than a mile**	[1]	[2]	[3]
8.	Walking **several blocks**	[1]	[2]	[3]
9.	Walking **one block**	[1]	[2]	[3]
10.	Bathing or dressing yourself	[1]	[2]	[3]

Modified Medical Research Council (mMRC) dyspnea (breathlessness) scale

Please circle the number which best describes your grade of breathlessness.

I only get breathless with strenuous exercise.	0
I get short of breath when hurrying on level ground or walking up a slight hill.	1
On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.	2
I stop for breath after walking about 100 yards or after a few minutes on level ground.	3
I am too breathless to leave the house or I am breathless when dressing.	4

Patient Satisfaction Questionnaire

Please circle the number which best describes your satisfaction with Spiolto® Respimat®.

What is your overall satisfaction with the Spiolto® Respimat® treatment?

1	2	3	4	5	6	7
very dissatisfied	dissatisfied	rather dissatisfied	neither satisfied nor dissatisfied	rather satisfied	satisfied	very satisfied

How satisfied are your with inhaling from the Respimat® device (e.g. feeling of inhalation, ease of inhalation, speed of inhalation)?

1	2	3	4	5	6	7
very dissatisfied	dissatisfied	rather dissatisfied	neither satisfied nor dissatisfied	rather satisfied	satisfied	very satisfied

How satisfied are your with the handling of the Respimat® inhalation device?

1	2	3	4	5	6	7
very dissatisfied	dissatisfied	rather dissatisfied	neither satisfied nor dissatisfied	rather satisfied	satisfied	very satisfied

Physicians' Global Evaluation (PGE) to be used directly within the eCRF

General condition of the patient at the initial examination (Visit 1)
Please mark with a cross as applicable

Poor	Satisfactory	Good	Excellent
1 2	3 4	5 6	7 8

General condition of the patient after approximately 6 weeks of treatment (Visit 2)
Please mark with a cross as applicable

Poor	Satisfactory	Good	Excellent
1 2	3 4	5 6	7 8