Non-interventional Study Protocol

Document Number:	c13799423-02
BI Study Number:	1237.60
BI Investigational Product(s):	Vahelva® Respimat® (Tiotropium bromide + Olodaterol hydrochloride)
Title:	A regulatory required non interventional study to monitor the safety and effectiveness of once daily treatment of orally inhaled Vahelva® Respimat® (Tiotropium + Olodaterol fixed dose combination 2.5µg/2.5µg per puff (2 puffs comprise one medicinal dose)) for Korean patients with COPD (Chronic Obstructive Pulmonary Disease)
Brief lay title	Vahelva® Respimat® rPMS in Korean patients with COPD
Protocol version identifier:	2.0
Date of last version of protocol:	*Not applicable*
PASS:	Yes
EU PAS register number:	EUPAS14956
Active substance:	Tiotropium bromide Olodaterol hydrochloride
Medicinal product:	Tiotropium + Olodaterol fixed dose combination solution for inhalation-Respimat®
Product reference:	*Not applicable*
Procedure number:	*Not applicable*
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	To monitor the safety profile and effectiveness of Vahelva® Respimat® (tiotropium + olodaterol) in Korea patients with COPD (Chronic Obstructive Pulmonary Disease) in a routine clinical practice setting

Country(-ies) of study:	Multi-Centre study conducted in Korea
Author:	[redacted] Phone: [redacted] Fax: [redacted]
Marketing authorisation holder(s):	[redacted]
MAH contact person:	[redacted]
EU-QPPV:	[redacted]
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically
Date:	08 October 2020
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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
BD	Bronchodilator
BI	Boehringer Ingelheim
BP	Blood Pressure
CA	Competent Authority
CML	Local Clinical Monitor
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
EU PAS	European Union Post-Authorization Safety
EU-QPPV	European Union – Qualified Person for Pharmacovigilance
FDC	Fix Dose Combination
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GPP	Good Pharmacy Practice
IC50	Inhibitory Concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
KNHANES	Korean National Health and Nutrition Examination Survey
LPVM	Local PV Manager

MAH	Marketing Authorisation Holder Activities
MedDRA	Medical Dictionary for Drug Regulatory Activities
MFDS	The Ministry of Food and Drug Safety
NCE	New Chemical Entity
NIS	Non-Interventional Study
NSADR	Non Serious Adverse Drug Reaction
OPU	Operative Unit
PASS	Post Authorization Safety Studies
PFT	Pulmonary Function Test
PMS	Post Marketing Surveillance
rNIS	Regulatory Non-Interventional Study
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TMF	Trial Master File
TMM	Team Member Medicine

3. RESPONSIBLE PARTIES

Boehringer Ingelheim(BI) has appointed a Trial Clinical Monitor(TCM), responsible for coordinating all required activities, in order to

- Manage the study in accordance with applicable regulations and internal standard operating procedures(SOPs).
- Direct the study team in the preparation, conduct, and reporting of the trial,
- Order the materials as needed for the study,
- Ensure appropriate training and information of Local Clinical Monitors(CMLs), Clinical Research Associate(CRAs), and Investigators of participating countries.

Data Management and Statistical Evaluation will be done by CRO according to CRO's SOPs.

The organization of the study in the participating countries will be done by the respective local BI- operative unit(OPU) or by a Contract Research Organization(CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the study. In each local BI OPU participating in this study, a CML will be appointed responsible for coordinating the activities required in order to manage the study in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU. On-site monitoring will be performed by BI or a CRO appointed by BI.

An Investigator Site File(ISF) containing all relevant study related documentation will be maintained according to local regulations and BI SOPs at each study site. A copy of the ISF documents will also be kept as an electronic Trial Master File(TMF) at BI according to BI SOPs. Documents related to participating physician and other important participants, especially their curricula vitae, will be filed in the TMF.

4. ABSTRACT

Name of company: [redacted]			
Name of finished medicinal product: Vahelva® Respimat®			
Name of active ingredient: Tiotropium + Olodaterol fixed-dose combination solution for inhalation - Respimat®			
Protocol date: 09 November 2016	**Study number:** 1237.60	**Version/Revision:** 2.0	**Version/Revision date:** 08 October 2020
Title of study:	A regulatory required non interventional study to monitor the safety and effectiveness of once daily treatment of orally inhaled Vahelva® Respimat® (Tiotropium + Olodaterol fixed dose combination 2.5µg/2.5µg per puff(2 puffs comprise one medicinal dose)) for Korean patients with COPD(Chronic Obstructive Pulmonary Disease)		
Rationale and background:	According to the local regulations, when a new chemical entity(NCE) is registered, a regulatory non interventional study(NIS) of an extended period(6 years) should be conducted. Such rNIS can provide supplementary data to monitor the safety of NCEs in a real-world situation. Data collected in randomized clinical study with strict inclusion/exclusion criteria and rigorous monitoring schemes have limitations.		
Research question and objectives:	To monitor the safety profile and effectiveness of Vahelva® Respimat® in Korean patients with COPD in a routine clinical practice setting		
Study design:	Observational prospective, non-interventional, open-label, multi-centre study		
Population:	Patients diagnosed with COPD will be included. Inclusion criteria: • Patients who have been started on Vahelva® Respimat® in accordance with the approved label in Korea • Age ≥ 18 years at enrolment • Patients who have signed on the data release consent form Exclusion criteria: • Patients with hypersensitivity to Vahelva® Respimat® or to any of the excipients. • Patients with a history of hypersensitivity to atropine or its derivatives(e.g. ipratropium, oxitropium, glycopyrronium, aclidinium, umeclidinium) • Patients with asthma • Current participation in other clinical trials Patients for whom Vahelva® Respimat® is contraindicated according		

Name of company: [redacted]			
Name of finished medicinal product: Vahelva® Respimat®			
Name of active ingredient: Tiotropium + Olodaterol fixed-dose combination solution for inhalation - Respimat®			
Protocol date: 09 November 2016	**Study number:** 1237.60	**Version/Revision:** 2.0	**Version/Revision date:** 08 October 2020
	local label of Vahelva® Respimat®.		
Variables:	Outcomes of safety All reported adverse events in patients who take at least once of Vahelva® Respimat® will be noted. Outcomes of effectiveness Change from baseline in (pre-dose) $FEV_{1,}$ (Post Bronchodilator Predicted %) FEV1, mMRC scale after 24±2 weeks and/or 52±2 weeks, conditionally. And overall evaluation after 24±2 weeks and/or 52±2 weeks of treatment will be noted.		
Data sources:	Field study with new data collection		
Study size:	N=3,000 approximately Sample size of 3,000 patients is based on the requirement of the local regulatory authority (MFDS).		
Data analysis:	In this non-interventional study, all statistical analyses will be descriptive. Data of characteristics and other status of patients will be described and proportions including the confidence intervals will be provided.		
Milestones:	Study duration: 6 years (MFDS sets Vahelva® Respimat® re-examination period from 31 August 2015 to 30 Aug 2021. Interim report planned biannually for the initial two years and annually thereafter by November 2021.		

4.1 FLOW CHART

Data points	**Baseline**	**Follow-up 1**	**Follow-up 2**
Visit Number	1	2	3
Week/s	0	24±2	52±2
Informed consent	X		
Diagnosis	X		
Inclusion / exclusion criteria	X		
Demographics	X		
Medical history	X		
PFT value - FEV_1/FVC pred (%) - (Pre-dose) FEV_1	X		
Physical examination	X	X	X
Concomitant medications	X	X	X
Vahelva® Respimat® administration status	X	X	X
(Pre-dose) FEV_1	X	X^A	X^A
(Post Bronchodilator Predicted %) FEV_1	X	X^A	X^A
Assessment of mMRC scale	X^A	X^A	X^A
Laboratory data	X^A	X^A	X^A
Adverse events		X	X
Study completion		X	X
Overall evaluation		X^A	X^A

A : If applicable

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
2	17 September 2020	9.2.3.2 visit 1 – Baseline visit	Effectiveness outcomes: (pre-dose) FEV1, BDI(within 1 month(30 days) prior to baseline date) *Was changed to:* Effectiveness outcomes: (pre-dose) FEV1, (Post Bronchodilator Predicted %) FEV1, mMRC scale(within 1 month(30 days) prior to baseline date)	Reflect to HA's feedback and epidemiology team's feedback
2	17 September 2020	9.2.3.3 Visit 2 - 24±2 weeks from Visit 1	Effectiveness assessment: (pre-dose) FEV1, TDI *Was changed to:* Effectiveness assessment: (pre-dose) FEV1, (post bronchodilator predicted %) FEV1, mMRC scale	Reflect to HA's feedback and epidemiology team's feedback
2	17 September 2020	9.2.3.4 Visit 3 - 52±2 weeks from Visit 1	Effectiveness assessment: (pre-dose) FEV1, TDI *Was changed to:* Effectiveness assessment: (pre-dose) FEV1, (post bronchodilator predicted %) FEV1, mMRC scale	Reflect to HA's feedback and epidemiology team's feedback
2	17 September 2020	9.3.2.1.1 Main outcome	Change from baseline in (pre-dose) FEV1 after 24 weeks and/or 52 weeks of treatment *Was changed to:* Change from baseline in (Post Bronchodilator Predicted %) FEV1 after 24 weeks and/or 52 weeks of treatment	Reflect to HA's feedback and epidemiology team's feedback
2	17 September	9.3.2.1.2 Other	Change from baseline in TDI after 24 weeks and/or 52	Reflect to HA's feedback and

	2020	outcomes	weeks of treatment *Was changed to:* Change from baseline in Pre-dose FEV1 after 24 weeks and/or 52 weeks of treatment Change from baseline in mMRC score after 24 weeks and/or 52 weeks of treatment	epidemiology team's feedback
2	17 September 2020	9.3.2.2 Assessment of Effectiveness	· (pre-dose) FEV1 (Forced Expiratory Volume in one second): (pre-dose) FEV1 should be collected within 1 month(30 days) prior to baseline and after 24 weeks and/or 52 weeks of treatment. · BDI/TDI(Baseline Dyspnea Index/Transition Dyspnea Index): BDI/TDI should be collected within 1 month(30 days) prior to baseline and after 24 weeks and/or 52 weeks of treatment. · Overall evaluation: Overall evaluation will be assessed after 24 weeks or 52 weeks of treatment. *Was changed to:* · Post Bronchodilator Predicted % FEV1(Forced Expiratory Volume in one second): Post BD FEV1 should be collected within 1 month(30 days) prior to baseline and after 24 weeks and/or 52 weeks of treatment. · (pre-dose) FEV_1 (Forced Expiratory Volume in one second): (pre-dose) FEV_1 should be collected within 1 month(30 days) prior to baseline and after 24 weeks and/or 52 weeks of	Reflect to HA's feedback and epidemiology team's feedback

			treatment. · mMRC scale: mMRC scale should be collected within 1 month(30 days) prior to baseline and after 24 weeks and/or 52 weeks of treatment. · Overall evaluation: Overall evaluation will be assessed after 24 weeks or 52 weeks of treatment.	

6. MILESTONES

Milestone	Planned Date
Start of data collection	30 Jul 2016
End of data collection	30 Aug 2021
Interim report 1	30 Apr 2016
Interim report 2	30 Oct 2016
Interim report 3	30 Apr 2017
Interim report 4	30 Oct 2017
Interim report 5	30 Oct 2018
Interim report 6	30 Oct 2019
Interim report 7	30 Oct 2020
Registration in the EU PAS register	29 Aug 2016
Final report of study results:	30 Nov 2021

7. RATIONALE AND BACKGROUND

7.1 RATIONALE

According to the local regulations, when a new chemical entity(NCE) is registered, a regulatory non interventional study(NIS) of an extended period(6 years) should be conducted. Such rNIS can provide supplementary data to monitor the safety of NCEs in a real-world situation. Data collected in randomized clinical study with strict inclusion/exclusion criteria and rigorous monitoring schemes have limitations.

This is an open-label, multi-centre and national non-interventional study based on newly collected data. It will provide additional safety information of Vahelva® Respimat® (Tiotropium + Olodaterol) in Korean patients with COPD(Chronic Obstructive Pulmonary Disease) in a routine clinical practice setting.

7.2 BACKGROUND

Chronic obstructive pulmonary disease(COPD) is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. COPD prevalence, morbidity and mortality vary across countries and across different groups within countries[P12-01205].

The prevalence of COPD in Korea increased from 12.5% in 2011 to 13.7% in 2012 and 12.8% in 2013. The Korean National Health and Nutrition Examination Survey(KNHANES, 2013) reported that approximately 12.8% of the population who were ≥40 years old. In addition, 27.7 of 100,000 persons die because of respiratory diseases, including COPD which was the fifth leading cause of death in Korea(Statistics Korea, 2009).

COPD is the result of cumulative exposure over decades; often, the prevalence of COPD is directly related to the prevalence of tobacco smoking, although in several countries, outdoor, occupational and indoor pollution are major risk factors.
The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the changing age structure of the world's population, with more people living longer and therefore expressing the long-term effects of exposure to COPD risk factors[P12-01205].

The combination of Tiotropium and Olodaterol in a single Respimat® Inhaler device provides a rational target for optimizing bronchodilator treatment of COPD.
Tiotropium(18μg) inhalation powder capsule (Spiriva®) has been approved in more than 100 countries worldwide as an antimuscarinic bronchodilator with a once daily posology. An alternative aqueous formulation for use in the Respimat® device (tiotropium 5μg qd) has recently been approved in Europe and Japan. Olodaterol, a long acting β2–agonist in clinical development(Phase III) by Boehringer Ingelheim, has a clinical profile with a 24-hour duration of action. The recently completed Phase III clinical program in COPD showed that Olodaterol at doses of 5μg and 10μg once daily is safe, well tolerated and efficacious; Olodaterol 5μg was identified as the optimal choice of dose for once daily maintenance

bronchodilator treatment in patients with COPD[U04-0202].

Safety data from the supportive Phase III 12 week trial and the 6-week crossover trials were consistent with the data from the 52-week pooled dataset. In conclusion, Tiotropium + Olodaterol 5/5µg and Tiotropium + Olodaterol 2.5/5µg delivered via the RESPIMAT inhaler were safe and well-tolerated in patients with moderate to very severe COPD[c01735808-12].

7.3 INDICATIONS

A maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease(COPD).

8. RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of this study is to monitor the safety profile of Vahelva® Respimat® (tiotropium + olodaterol fixed dose combination 2.5µg/2.5µg per puff (2 puffs comprise one medicinal dose)) in Korean patient with COPD in a routine clinical setting.

8.2 SECONDARY OBJECTIVE

The secondary objective of this study is to monitor the effectiveness of Vahelva® Respimat® (tiotropium + olodaterol fixed dose combination 2.5µg/2.5µg per puff (2 puffs comprise one medicinal dose)) by evaluation the change from baseline to outcome in the (pre-dose) FEV_1(Forced Expiratory Volume in one second), (Post Bronchodilator Predicted %) FEV_1(Forced Expiratory Volume in one second) and mMRC(Modified Medical Research Council) scale of Korean COPD patients.

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9. RESEARCH METHODS

This rNIS is an observational prospective, non-interventional, open-label, multi-centre and national study. As per regulation, the re-examination period extends from 31 August 2015 until 30 August 2021. However, active enrolment is to be initiated in 2016 after finalizing the re-imbursement agreement with the authority. Before initiation of the study, any newly reported adverse events collected from other sources such as spontaneous cases, literature cases etc will be closely monitored. The last patient follow up is expected in August 2021.

This study will be carried out in the manner of successive survey that the investigator will be asked to successively write in the case report forms(CRFs) from the subject who was initially administered the drug following the study start date to the requested number of subjects without omission. Prior to initiation of the study, written contract shall be concluded, and this contract shall be concluded with the head of the site or the investigator with his/her consent.

Patients will be managed according to the local practice guidelines. The choice of treatment will be solely at the discretion of the participating physician. Vahelva® Respimat® will be administered according to the approved label in Korea. Hence there are no additional risks to patients by participating in this rNIS.

9.1 STUDY DESIGN

This is a NIS based on newly collected data with Vahelva® Respimat®.
Vahelva® Respimat® will be prescribed according to the local label and at the discretion of the treating physician. Since this is a NIS, the drug will not be supplied by the sponsor. Furthermore, the sponsor will not cover the expenses related to other medications taken by the patient, interventions, procedures or diagnostic test.

9.1.1 Method of assigning patients to treatment groups

The choice of treatment is fully at the discretion of the physician and the patient. There is no treatment assignment by a third party.

9.1.2 Dosage and Administration

The starting dose is based on the current authorized label in Korea.
The recommended dose for adults is 5 microgram Tiotropium and 5 microgram Olodaterol given as two puffs from the Respimat® inhaler once daily at the same time of the day(see Instructions for Use).

9.1.3 Concomitant therapy, Restrictions, And rescue

The protocol will allow additional drugs considered necessary for the patient's welfare to be prescribed at the discretion of the treating physician. It is required, however, to record the details of all concomitant medication administered to the patient during the course of treatment in eCRF. This includes concomitant therapies started one month prior to Vahelva® Respimat® initiation until the patient completes the final follow-up visit.

9.1.3.1 Rescue medication, emergency procedures, and additional treatments

Please refer to the current local label.

9.2 SETTING

As per regulations, enrolled patients will be followed up for 24weeks or 52 weeks treatment period. There will be a visit window of ±2weeks.

9.2.1 Study sites

A total of 3,000 patients will be enrolled at approximately 50 sites by as many as 50 or more NIS physicians. To minimize the selection bias at the site level, the goal is to have participating centers reflect a balance between general hospitals and clinics for surveillance. The treating physicians will mainly be Respiratory Internists. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.

9.2.2 Study population

9.2.2.1 Main diagnosis for study entry

Patients diagnosed with COPD will be included.

9.2.2.2 Inclusion criteria

- Patients who are new initiators of Vahelva® Respimat® in accordance with the approved label in Korea
- Age ≥ 18 years at enrolment
- Patients who have signed on the data release consent form

9.2.2.3 Exclusion criteria

- Patients with hypersensitivity to Vahelva® Respimat® or to any of the excipients.
- Patients with a history of hypersensitivity to atropine or its derivatives (e.g. ipratropium, oxitropium, glycopyrronium, aclidinium, umeclidinium)
- Patients with asthma
- Current participation in other clinical trials
- Patients for whom Vahelva® Respimat® is contraindicated according to the local label of Vahelva® Respimat®

9.2.2.4 Subjects of special investigation

The patient who have signed on the data release consent form, subjects of special investigation(Pediatric or Adolescent(Younger than 18 years), Geriatric(Older than 65 years), Pregnant Women, renal impairment, hepatic impairment and other special population) among the patients who conducted investigation for safety assessment after the administration of Vahelva® Respimat® can be further investigation into cases collected from this study may be taken into account according to the outcome of retrospective analysis.

9.2.3 Study visits

9.2.3.1 Screening and run-in periods

This section is not applicable as this is a non-interventional study.

9.2.3.2 Visit 1 - Baseline Visit

Upon patient enrolment, the following will be recorded on the patient's eCRF.

- Visit date
- Informed consent form: Date of Informed consent
- Diagnosis: Date of the diagnosis of COPD
- Inclusion / Exclusion criteria
- Demographic data: Initial, year of birth(age), gender, pregnancy, previous allergy, height, weight, smoking status
- Medical history: history of cardiovascular disease, metabolic disease, respiratory disease, any malignancy, renal dysfunction and other concomitant disease within 6 months.
- Physical examination: Blood pressure, pulse rate, body temperature
- PFT value for diagnosis of COPD: FEV_1/FVC predicted (%), (pre-dose) FEV_1 (within 6 months(180 days) prior to baseline date)
- Effectiveness outcomes : (pre-dose) FEV_1, (Post Bronchodilator Predicted %) FEV_1, mMRC scale(within 1 month(30 days) prior to baseline date)
- Concomitant medications: Record all medications have been taken at least once since one month(30 days) prior to the baseline visit.
- Dose of Vahelva® Respimat® given

At visit 1, the patient will be requested to contact the treating physician in the event of any adverse events noted after initiating Vahelva® Respimat® treatment.

9.2.3.3 Visit 2 - 24±2 weeks from Visit 1

After 24±2 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the eCRF.

- Visit date
- Physical examination: Blood pressure, pulse rate, body temperature
- Effectiveness assessment: (pre-dose) FEV_1, (post bronchodilator predicted %) FEV_1, mMRC scale
- Any change of Vahelva® Respimat® given
- Concomitant medications including new medications taken since last visit : any change in the concomitant medications(dose and dosing intervals)
- Any changes in laboratory tests if there is any lab result which was clinically significant compared to data before Vahelva® Respimat® therapy (This data is collected on the basis of medical need, i.e. independent of the NIS)
- Any adverse events noted
- Study completion status

- Overall evaluation
- NIS physician's electronic signature for data integrity(if applicable)

9.2.3.4 Visit 3 - 52±2 weeks from Visit 1

After 52±2 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the eCRF.

- Visit date
- Physical examination: Blood pressure, pulse rate, body temperature
- Effectiveness assessment: (pre-dose) FEV_1, post bronchodilator predicted %) FEV_1, mMRC scale
- Any change of Vahelva® Respimat® given
- Concomitant medications including new medications taken since last visit: any change in the concomitant medications(dose and dosing intervals)
- Any changes in laboratory tests if there is any lab result which was clinically significant compared to data before Vahelva® Respimat® therapy (This data is collected on the basis of medical need, i.e. independent of the NIS)
- Any adverse events noted
- Study completion status
- NIS physician's electronic signature for data integrity

9.2.3.5 End of study and follow-up period

Patients with adverse events noted at the final follow-up visit or upon premature discontinuation of Vahelva® Respimat® will be monitored further until the resolution of those adverse events. Alternatively, those patients will be followed up until the NIS physician and sponsor agree that no further follow-up is necessary.

9.2.4 Study discontinuation

[redacted] reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

- Emergence of any effectiveness/safety information that could significantly affect continuation of the study
- Violation of applicable local regulations, the NIS protocol, or the contract by a study site or participating physician, disturbing the appropriate conduct of the study.

9.3 VARIABLES

9.3.1 Safety

9.3.1.1 Outcome(s) of safety

All reported adverse events in patients who take at least once of Vahelva® Respimat® will be noted.

Outcomes pertaining to safety will be presented as incidence rates of adverse events and will include:

- Adverse events
- Unexpected adverse events
- Serious adverse events
- Adverse Drug Reactions
- Adverse events leading to discontinuation
- Adverse events by intensity, outcome of the events, causality

9.3.2 Effectiveness

9.3.2.1 Outcome(s) of effectiveness

9.3.2.1.1 Main outcome

- Change from baseline in (Post Bronchodilator Predicted %) FEV_1 after 24 weeks and/or 52 weeks of treatment

9.3.2.1.2 Other outcomes

- Change from baseline in Pre-dose FEV_1 after 24 weeks and/or 52 weeks of treatment
- Change from baseline in mMRC score after 24 weeks and/or 52 weeks of treatment
- Overall evaluation(Improved, unchanged, aggravated or unassessible) by investigator based on overall clinical assessment including change from baseline in effectiveness assessment((Post bronchodilator predicted % of) FEV1, (pre-dose) FEV_1, mMRC scale) after 24 weeks or 52 weeks of treatment. 'Improved' is assessed as "Effective", 'Unchanged, Aggravated' are assessed as "Invalid".

9.3.2.2 Assessment of Effectiveness

- Post Bronchodilator Predicted % FEV1(Forced Expiratory Volume in one second): Post BD FEV1 should be collected within 1 month(30 days) prior to baseline and after 24 weeks and/or 52 weeks of treatment.
- (pre-dose) FEV_1 (Forced Expiratory Volume in one second): (pre-dose) FEV_1 should be collected within 1 month(30 days) prior to baseline and after 24 weeks and/or 52 weeks of treatment.
- mMRC scale: mMRC scale should be collected within 1 month(30 days) prior to baseline and after 24 weeks and/or 52 weeks of treatment.
- Overall evaluation: Overall evaluation will be assessed after 24 weeks or 52 weeks of treatment.

9.3.3 Items of Investigation

9.3.3.1 Demographic data

For demographic evaluation, following background information of subjects shall be recorded:

- Subject signed date
- Subject study number
- Initial
- Gender
- Pregnancy
- Height
- Weight
- Year of birth(age)
- Smoking status

9.3.3.2 Medical history

The medical history to be collected prior to administration of this drug includes:

- Check hepatic or renal impairment
- Diagnosis
- Severity(Mild, Moderate, Severe)
- Date of diagnosis or date of surgery
- End date or continuation

9.3.3.3 Concomitant medication

Information on concomitant medication that is to be collected includes:

- Brand name
- generic name
- Route of medication
- Daily dose
- Unit
- Purpose of administration
- Indication
- Start date
- Date of discontinuation or continuation

9.3.3.4 Drug administration status

Information on the drug administration status includes:

- Dose
- Unit
- Start date
- Date of discontinuation or continuation

9.3.3.5 Information on the site

Information on the site includes:

- Hospital name
- Department
- Physician name

9.3.3.6 Result of laboratory tests(if applicable)

Information on the result of laboratory tests includes:

- Name of lab test
- Range of normal(Unit, Maximum and minimum data)
- Result of lab test before treatment
- Result of lab test after treatment

9.3.3.7 Overall evaluation

Information on the overall evaluation includes:

- Improved: If determined as there is any effect of maintaining or improving symptoms.
- Unchanged: If symptoms have not been changed compared with before administration, and not determined as there is any effect of maintaining symptoms.
- Aggravated: If symptoms are worse than before administration.
- Unassessible: If it cannot be determined due to insufficient information collected(Even though there are any objective indicators present, it is possible to belong to this grade.).

9.3.4 Outcomes of subjects Evaluation

9.3.4.1 Subject evaluation items

9.3.4.1.1 Number of cases who accepted the study

This number means the planned number of cases as specified in the contract concluded with the investigator(physician) prior to initiation of the study.

9.3.4.1.2 Number of cases subject who collected CRF

This number means the number of cases who signed the informed consent form to participate in the study as subject, and have record of taking Vahelva® Respimat® once at least.

9.3.4.1.3 Number of dropouts

These cases include those who signed the informed consent form to participate in this study as subject but did not meet any of the inclusion criteria, do not have any prescription record of Vahelva® Respimat®, have prescription record but have not been followed up by the physician following prescription and started administration prior to the signed date.

9.3.4.1.4 Number of cases subject to safety evaluation

These cases include those who signed the informed consent form to participate in this study as subject, took Vahelva® Respimat® once at least, and were completed follow up by the physician once or more.

9.3.4.1.5 Number of cases subject to effectiveness evaluation

These cases include those who signed the informed consent form to participate in this study as subject, visited as per the study schedule, took Vahelva® Respimat®, the cases included in safety evaluation, and were evaluated for the effectiveness including overall evaluation(if the case assessed as 'unassessible' will be excluded).

9.3.4.1.6 Subjects of special investigation

The patient who have signed on the data release consent form, subjects of special investigation(Pediatric or Adolescent(Younger than 18 years), Geriatric(Older than 65 years), Pregnant Women, renal impairment, hepatic impairment and other special population) among the patients who conducted investigation for safety assessment after the administration of Vahelva® Respimat® can be further investigation into cases collected from this study may be taken into account according to the outcome of retrospective analysis.

9.4 DATA SOURCES

This study will be carried out in the manner of successive survey that the investigator will be asked to successively write in the case report forms(CRFs) from the subject who was initially administered the drug following the study start date to the requested number of subjects without omission. Prior to initiation of the study, written contract shall be concluded, and this contract shall be concluded with the head of the site or the investigator with his/her consent.

9.5 STUDY SIZE

Sample size of 3,000 patients is based on the requirement of the local regulatory authority (MFDS). Since COPD is chronic disease it might be restrictive to collect data in just short-term (24±2weeks) period. The local regulatory authority(MFDS) recommends long-term(at least 52±2weeks) surveillance for maintaining approved indication. Thus all patients will be enrolled for long-term(52±2weeks) surveillance, basically.
Considering total surveillance size of 3,000 cases, at least 20%(600 cases) of total would be enrolled for long-term(52±2weeks) surveillance, even considering follow up loss in real world practice. Every institution will be contract for only one option of follow up period(short-term surveillance or long-term surveillance). It will be decided by feasibility check before to decide participation.

9.6 DATA MANAGEMENT

Patients' data will be gathered by eCRF. The data management procedures to ensure the quality of the data are described in detail in the data management plan (DMP) available in TMF. Data management and statistics will be outsourced to a qualified contract research organization (CRO).

9.7 DATA ANALYSIS

The safety evaluation will be performed on the "safety set" that will include all patients who have received treatment of Vahelva® Respimat® at least one time except those who are found to have no observation after enrolment, invalid registration, or invalid contract with the site. The effectiveness evaluation will be performed on the "effectiveness set", a subset of the safety set, which will include all patients in the "safety set" except those who have no available effectiveness data and/or who do not suffer from COPD.
Medico-pharmaceutical assessment will be described with results of multiple regression analysis, 95% confidence intervals of every sub-analysis items of safety and effectiveness assessment.
Details are provided in the Statistical Analysis Plan (SAP).

9.7.1 Statistical design – model

In this NIS, all statistical analyses will be descriptive.
The level of statistical significance (p-value) and the precision (confidence interval) for the statistical analysis method used for exploratory purposes will be presented. Confirmatory hypothesis will not be conducted.

9.7.2 Demographic baseline data

Descriptive statistics will be performed that is data of demographics and medical health status of safety assessed cases. Average, standard deviation, min value, max value and median will be displayed for continuous data. The frequency will be conducted from categorical data.

Baseline characteristics (Demographics(all), co-morbidity, initial (pre-dose)FEV_1, (post bronchodilator predicted % of) FEV1, mMRC, co-medications, etc.) will be compared between the "long-term group" (patients who will be followed up for 52 weeks) and the "short-term group" (patients who will be followed up for 24 weeks) to put the data into perspective.

9.7.3 Analysis of Safety

Demographic and baseline characteristics will be summarized descriptively for the entire cohort of eligible patients.

Adverse events(AEs) from demographic data of safety assessment cases;

- Number of subjects and cases of AEs will be counted and incidence rate, 95% CI calculation.
- Calculate 95% confidence interval and rate of AEs. Analysis by one of methods of chi square test, fisher's exact test or logistic regression analysis methods in each item to find difference of AEs' rate or find factor that influence to safety profile.

Adverse Events (AEs) will be coded according to the latest version of Medical Dictionary for Drug Regulatory Affairs (MedDRA) coding system. The study database will not be locked until coding is complete.

Safety analyses will be based on all patients treated, i.e. all patients who received at least one dose of Vahelva® Respimat®. However, if data for patients who have been treated with Vahelva® Respimat® beyond the scope of approved label are collected, separate safety analyses will be performed. Safety analyses will be performed based on demographics and baseline characteristics.

Patients lost to follow up will be characterized compared to the remaining patients and reason and time point of loss to follow up will be evaluated.

9.7.4 Analysis of Effectiveness

Effectiveness assessment of short-term and long-term cases will be analysis. Effectiveness rate and 95% confidence interval of demographic data will be calculated. One of methods of chi square test, fisher's exact test or logistic regression analysis methods will be use appropriately.

9.7.4.1 Main outcome analyses

A descriptive analysis of effectiveness outcomes is planned. For patients treated with Vahelva® Respimat®, the change of Post Bronchodilator Predicted % FEV1 from baseline and last follow-up visit will be calculated. Effectiveness analysis will be performed based on demographic characteristics and baseline characteristics.

9.7.4.2 Other outcome analyses

A descriptive analysis of effectiveness outcome is planned. For patient treated with Vahelva Respimat, the change of (pre-dose) FEV_1 from baseline and last follow up visit will be calculated. Effectiveness analysis will be performed based on demographic characteristics and baseline characteristics.
A descriptive analysis of effectiveness outcome is planned. For mMRC, descriptive statistics will be calculated. Effectiveness analysis will be performed based on demographic characteristics and baseline characteristics.
A descriptive analysis of effectiveness outcomes is planned. For overall evaluation, descriptive statistics will be calculated for assessed one of the items(improved, unchanged, worsen or not applicable) by investigator with medical opinion of each individual component and the changes from scores before first administration. Effectiveness analysis will be performed based on demographic characteristics and baseline characteristics.

9.7.5 Interim analyses

In accordance with local regulation for rNIS, interim analyses are planned biannually for the initial two years and annually thereafter.

9.7.6 Handling of missing data

As this is a NIS, there are no required investigations and diagnostic procedure (e.g. lab, ultrasound).

Maximum attempt will be made to ensure the completeness of data collection. All available data will be used in the data analysis. Missing or incomplete AE dates are imputed according to BI standard.

9.8 QUALITY CONTROL

All entries in the eCRF and the existing coding will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the eCRF. To improve and ensure data quality, data checks will be performed automatically in the eCRF directly on electronic entry at the study site.
Plausible value ranges for numerical data entries and logical data and list entries will be filed in the eCRF. The tests for consistency and completeness based on this will be performed during entry in the eCRF. The validity of the recorded data will therefore be ensured by the validations incorporated in the documentation system, which highlight incorrect or implausible entries to the data entry clerk/doctor.
If corrections are necessary after the data are saved, these will be documented in an audit trail.
For the further quality assurance of the documented patient observations, a sample-based source data comparison might be performed on about 10% of the sites. An additional inspection/quality assurance check of this NIS can be performed in case of any deviation.

9.9 LIMITATIONS OF THE RESEARCH METHODS

9.9.1 Follow up loss

All efforts will be made to minimize lost to follow up, particularly in the tracking of lost patients. To the extent possible, occurrence of adverse event, at minimum, for patients lost to follow up will be obtained. This allows assessing the impact of informative censoring due to treatment discontinuation. Also, patients lost to follow up will be characterized compared to the remaining patients and reason and time point of loss to follow up will be evaluated.

9.9.2 Channeling bias

Channeling bias can occur due to preferential prescribing in relation to different risks for the events of interest: e.g., if Vahelva® Respimat®(tiotropium + olodaterol) would be more often prescribed to higher risk patients compared to other treatments, higher incidences of outcome events were then expected in the Tiotropium + Olodaterol group.

9.9.3 Confounding

As in any NIS, confounding may affect the estimation of associated between drug exposure and outcome of interest and statistical techniques. However, as only major confounders for selected research questions can be captured, residual (unmeasured) confounding may remain.

9.10 DATA PROTECTION, STUDY RECORDS

The International Conference on Harmonization/Harmonized Tripartite Guideline for Good Clinical Practice (ICH/GCP) does not often apply to NIS as most elements are relevant for

controlled clinical trials. However, in this NIS, all attempts will be made to adhere, as close as possible, to the standards of ICH/GCP.

The protocol of this regulatory requisite NIS will be submitted to the Ministry of Food And Drug Safety (MFDS) for notification. It is not a local requirement in Korea to obtain Institutional Review Board (IRB) approval for the conduct of regulatory requisite NIS. All of sites will be selected which has own IRB in hospital. The protocol of this NIS will be submitted to IRBs whenever required or requested by these institutions. This study will be conducted in accordance with the Standards for Re-examination of New Medicines notified by MFDS, Korean Pharmaceutical Affairs Code (KPAC), Enforcement Regulation of KPAC and other applicable local laws and industry code (including but not limited to the Regulations on Fair Competition in the Trade of Medicines of KPMA and KRPIA).

[redacted] will submit periodic reports during re-examination period, and the final report to MFDS upon study completion. The periodic report for the final year will be substituted with the final report. When required, the interim reports and the final report will be submitted to the IRBs as well.

9.10.1 Data quality assurance

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

9.10.2 Study records

All of the clinical data will be captured via a web-based EDC (Electronic Data Capture) 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. The treating physician will approve the data using an electronic signature.
Patients will not be identified on the eCRF by name. Appropriate code identification (i.e., patient number) will be used. The treating physician will make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in this study in case follow-up is required. Likewise, any supporting documentation will be redacted of any patient identifying information, and the patient ID number clearly written on the documents.

9.10.2.1 Source documents

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

Data reported on the eCRFs must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study; current medical records must also be available.

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

- Patient identification(gender, age, initial)
- Patient participation in the study(study number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of study medication
- Medical history(including study indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events(onset date(mandatory), and end date(if available))
- Serious adverse events(onset date(mandatory), and end date(if available))
- Concomitant therapy(start date, changes)
- Laboratory results(if applicable)
- Completion of Patient's Participation in the study

9.10.2.2 Direct access to source data and documents

The Investigator / institution will permit study-related monitoring, audits, IRB review and regulatory inspection, providing direct access to all related source data / documents. eCRF and all source documents must be available at all times for review by the Sponsor's non interventional study specialist(NIS specialist), auditor and inspection by health authorities (e.g. MFDS). The NIS specialist and auditor may review all eCRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in section 9.10.2.1.

9.10.2.3 Storage period of records

The NIS physician and the site are jointly responsible for maintaining essential study documents for 3 years after completion of the study (defined as termination date of re-examination period) by the Pharmaceutical Affairs Law and shall take measures to prevent accidental or premature destruction of these documents.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the applicable sections of GCP, relevant BI Standard Operating Procedures and local regulations. 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/International Conference on Harmonization(ICH) GCP / GPP if applicable.
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.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board(IRB) / Independent Ethics Committee(IEC) 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(or the patient's legally accepted representative) according to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent 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 BI 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(NIS Specialist) or Clinical Quality Assurance auditors appointed by BI, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study will be considered confidential and disclosure to third parties will be prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. Treatment data will be made available to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated from the study will be made available for inspection on request by the participating physicians, the sponsor and/or its representatives and/or designees, by the IRBs/IECs and the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An 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 AE 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 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 authorisation 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(SAE) is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity,
- 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 jeopardise 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.

Non Serious Adverse Drug Reaction
Non Serious Adverse Drug Reaction(NSADR) is defined as any adverse reaction which does not meet the SAE criteria.

AESI (Adverse Event of Special interest)

No AESI (Adverse Event of Special interest) 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 studies are available to support the evidence on the safety and effectiveness of the studied Vahelva® Respimat®. For this reason the following AE collection and reporting requirements have been defined.

Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the site materials (that include all necessary documents, the protocol, instructions for conducting NIS, the package insert etc.).

All adverse events occurred from the signing date on data release consent form to last visit date of monitoring period need to be collected, documented and reported to the sponsor using the AE page of eCRF(Attachment 1). It will then be automatically reported to the sponsor via email as 'AE Alert'. All SAEs must be reported with details of relevant non-serious AEs, within 24 hours of occurrence via Electronic Data Capture system to the Local PV Manager(LPVM) of [redacted] using the NIS AE report form(Attachment 2). If any new or further information to these events is available, a follow-up NIS AE report has to be sent to BI. All SAEs and non-serious AEs must include a causal relationship assessment from the physician.

Contact details:
Local PV Manager(LPVM)
Tel: [redacted]
Fax: [redacted]
Address: [redacted] (Postal code: [redacted]

The investigator carefully assesses whether an AE constitutes an Adverse Reaction using the information below.

Causal relationship of AEs
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterised 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.

The causal relationship must be provided by the Investigator for all potential study drugs, i.e. the BI study drug and for all other study drugs.
The reason for the decision on causal relationship needs to be provided in the (e)CRF and on the NIS AE form (if applicable).

Related

a. Certain: An event occurring in a plausible time relationship to drug administration and that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary,

b. Probable/Likely: An event with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal(dechallenge). Rechallenge information is not required to fulfill this definition.

c. Possible: An event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

d. Conditional/Unclassifiable: Case of requiring more data or reviewing the additional data for the appropriate assessment

e. Unassessable/ Unclassifiable: Case that it cannot be judged and complemented or confirmed due to the insufficient or contradictory information

Unrelated

a. Unlikely: An event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Intensity of AE

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 study medication, VAHELVA® 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's LPVM 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.

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form and not the NIS AE form is to be completed. If there is an SAE associated with the pregnancy then the SAE has to be reported on the NIS AE form in addition.

The ISF will contain the Pregnancy Monitoring Form (Part A and B).

Expedited Reporting of AEs and Drug Exposure During Pregnancy

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

Type of Report	Timeline
All **Serious Adverse Events** (SAEs)	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Vahelva® Respimat® (Tiotropium + Olodaterol)	immediately within 24 hours

All **non-serious Adverse Drug Reaction** associated with Vahelva® Respimat® (Tiotropium + Olodaterol)	7 calendar days
All Drug exposure during pregnancy	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 the AE page of the eCRF.

Information required
For each reportable AE, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE form.

Reporting of related AEs associated with any other BI drug
The investigator is encouraged to report all adverse events related to any BI drug other than Vahelva® 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 MAH according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

13. REFERENCES

13.1 PUBLISHED REFERENCES

P12-01205 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (revised 2011).

R96-2117 Mahler DA, Weinberg DH, Wells CK, Reinstein AR, The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 85(6), 751-758(1984)

13.2 UNPUBLISHED REFERENCES

U04-0202 [redacted]BI 1744 CL: Investigator's Brochure. 1222.P1.

c01735808-12 Tiotropium + Olodaterol fixed dose combination Investigator's Brochure

No. 0287-01 SPIOLTO® RESPIMAT® Company Core Data Sheet

13.3 WEB SITE

1. Korean National Health and Nutrition Examination Survey (2013) http://knhanes.cdc.go.kr

2. Statistics Korea: 2009 statistical results about cause of death. http:// www.index.go.kr

14. APPENDICES

14.1 ELECTRONIC CASE REPORT FORM

See the Attachment 1.

14.2 SAE/ NON-SERIOUS ADVERSE REACTION REPORT

See the Attachment 2.

14.3 PREGNANCY MONITORING FORM

See the Attachment 3.

14.4 VAHELVA® RESPIMAT® PRESCRIPTION INFORMATION FOR KOREA

See the Attachment 4.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
None			

ANNEX 2. MODIFIED MEDICAL RESEARCH COUNCIL(MMRC)

Difficulty breathing in daily life is evaluated by the mMRC level consisting of five scores, and it is divided into a score without difficulty breathing (score 0) and inability to live normal life (score 4).

Score	Level of Breathlessness
0	Only breathlessness with strenuous exercise
1	Shortness of breath hurrying or walking up a slight hill
2	Walks slower than age group or has to stop for breath when walking on level ground at own pace
3	Stops for breath after walking 100 meters or a few minutes on level ground
4	Breathless when dressing/undressing or too breathless to leave the house

ANNEX 3. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies).

Study title:
A regulatory required non interventional study to monitor the safety and effectiveness of once daily treatment of orally inhaled VAHELVA® RESPIMAT® (Tiotropium + Olodaterol fixed dose combination 2.5µg/2.5µg per puff (2 puffs comprise one medicinal dose) for Korean patients with COPD (Chronic Obstructive Pulmonary Disease)

Study reference number:
1237.XX

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection	☒	☐	☐	13
1.1.2 End of data collection	☒	☐	☐	13
1.1.3 Study progress report(s)	☒	☐	☐	13
1.1.4 Interim progress report(s)	☒	☐	☐	13
1.1.5 Registration in the EU PAS register	☒	☐	☐	13
1.1.6 Final report of study results.	☒	☐	☐	13

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	14
2.1.2 The objective(s) of the study?	☒	☐	☐	16
2.1.3 The target population? (i.e. population or	☒	☐	☐	18

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
subgroup to whom the study results are intended to be generalised)				
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	17
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	16
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	21

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	18
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	17
4.2.2 Age and sex?	☒	☐	☐	18
4.2.3 Country of origin?	☒	☐	☐	18
4.2.4 Disease/indication?	☒	☐	☐	18
4.2.5 Co-morbidity?	☒	☐	☐	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	18

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for	☒	☐	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
defining and categorising exposure)				
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	21
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	21

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including	☒	☐	☐	22

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
scales and questionnaires, vital statistics, etc.) 8.1.3 Covariates?	☒	☐	☐	22
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	23
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	23
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	18
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	25
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	25
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	24
10.2 Is the choice of statistical techniques described?	☒	☐	☐	24
10.3 Are descriptive analyses included?	☒	☐	☐	24
10.4 Are stratified analyses included?	☒	☐	☐	24
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	26
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	26

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	26
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	29
11.3 Are methods of quality assurance described?	☒	☐	☐	28
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	28
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	25
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	25
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	23
12.3 Does the protocol address other limitations?	☒	☐	☐	25

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	28
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	28
13.3 Have data protection requirements been described?	☒	☐	☐	28

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document	☐	☐	☐	

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
future amendments and deviations?				

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	33
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	36

Comments:

Name of the main author of the protocol: [redacted]

Date: 17/Sep/2020

Signature: [redacted]