Protocol - MA-PY-HpPK11-01

A Safety and Pharmacokinetic study in Real-life practice of Pylera® in France: The SAPHARY Study

Study Phase: Phase IV

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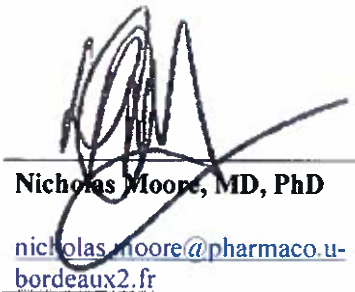
Université de Bordeaux, Scientific leader:		04/11/2013	
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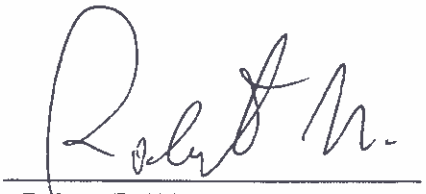
Aptalis Pharma US, Inc. Vice President, Global Clinical Development and Operations:			
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STUDY SYNOPSIS

Study Title:	A **Sa**fety and **Pha**rmacokinetic study in **R**eal-life practice of P**y**lera® in France: The SAPHARY Study
Name of test drug / investigational product	Not applicable
Objectives:	***Primary Objective:*** To verify the absence of accumulation of bismuth in subjects prescribed Pylera®, a pharmacokinetic approach in a real-life setting. ***Secondary Objectives:*** 1. To evaluate treatment effectiveness by the eradication measured by a negative diagnostic *H. pylori* test (breath test, biopsy, or other test at the discretion of the Investigator) for subjects with an initially positive *H. pylori* test. 2. To compare post-treatment bismuth concentrations in treatment successes and failures. 3. To evaluate the accumulation of bismuth in subjects receiving Pylera® with omeprazole *versus* subjects who received Pylera® with another proton pump inhibitor (PPI). 4. To compare safety data profiles in treatment successes and failures.
Study Description:	Open-label, single-arm, multicenter, trial restricted to centers in France.
Initiation Date: ***Completion Date:***	This study has an anticipated recruitment period of 24 months, with the recruitment Initiation Date (First Subject, First Visit) expected to be within 6 calendar months of the launch of Pylera® in France. The recruitment Completion Date (Last Subject, First Visit) is expected to occur 24 months following study start (approximately 30 calendar months from marketing launch). Eligible subjects will stay in study for approximately 6 weeks.
Study Population:	Two hundred (200) men and women 18 years of age and older who meet the following criteria: ***Inclusion Criteria:*** 1. Men and women 18 years of age and older who have received a prescription for Pylera® therapy from the Investigator 2. Mental and legal ability to give written Informed Consent and judged by

	the Investigator to be capable of following the procedures outlined within the protocol ***Exclusion Criteria:*** 1. Women who are pregnant or nursing 2. Any concern by the Investigator regarding the safe participation of the subject in the study or for any other reason the Investigator considers the subject inappropriate for participation in the study
Study Drug Administration:	Not Applicable. This study is intended as a PK assessment of bismuth in subjects already prescribed Pylera® in real-life practice.
Study Procedures:	This is a single-arm, open-label trial in presumed *H. pylori*-positive subjects and is restricted to centers in France. Following identification of participating general practice and specialist study centers, subjects deemed eligible for study will be identified and may be enrolled. To assess eradication, subjects will complete a diagnostic *H. pylori* test (breath test, biopsy, or other test at the discretion of the Investigator) following a period of at least 28 days after the end of treatment. Subjects who are treatment-eligible will already have a prescription for Pylera® and a PPI (presumed to be omeprazole) and will have been instructed on dosing as the dosing information contained within the Pylera® SmPC: 3 capsules Pylera® QID taken after meals and following a bedtime snack, and omeprazole capsule BID taken after breakfast and evening meal doses of Pylera®, for 10 days (equivalent to daily doses of 480 mg [as Bi_2O_3 equivalent], tetracycline hydrochloride 1500 mg, metronidazole 1500 mg, and omeprazole 40 mg). Subjects will provide two blood samples for assessment of bismuth concentrations (total bismuth in plasma and whole blood and trimethylbismuth (TMB) in whole blood), with one sample provided prior to start of Pylera® treatment (D0) and one sample provided Day 11 i.e. Day 1 after completion of Pylera® treatment. If accumulation of bismuth is detected (defined as whole blood bismuth concentration exceeding 50 µg/L.), subjects will be contacted to immediately return to the laboratory to draw a third verification sample and will be referred for potential inclusion and follow-up in a separate intensive monitoring program. In case of a neurological AE indicative of bismuth encephalopathy (please refer to Appendix 3 – Central Nervous System Adverse Events of Interest) is present at Day 11 blood samples will be as quickly processed as possible.

	A diagnostic *H. pylori* test to assess *H. pylori* eradication should be repeated on one single occasion at least 28 days post-treatment.
Safety/Efficacy Variables:	***Safety Variables:*** The safety profile will be assessed in terms of overall AEs, vital signs, and concomitant medication usage over the 10-day treatment period, as well as at the 4 weeks follow-up period after treatment. There will be an additional follow-up for neurological adverse events (AEs) indicative of encephalopathy. ***Efficacy Variables:*** A post-treatment diagnostic result of *H. pylori* test for eradication (e.g. breath test, biopsy or other test at the discretion of the Investigator).
Pharmacokinetic considerations:	Pre- and post-treatment bismuth plasma and whole blood concentrations by participating subjects will be collected.

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LIST OF ABBREVIATIONS

Global list

AE	Adverse event
ARO	Academic Research Organization
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
EudraCT	New European Clinical Trials Database
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HPFB	Health Products and Food Branch
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Study File
ITT	Intent to treat
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
PhRMA	Pharmaceutical Research and Manufacturers of America
PI	Primary Investigator
PP	Per Protocol
PSUR	Periodic Safety Update Report
REB	Research Ethics Board
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
WHO	World Health Organization

Study Specific List

BID	Two Times a Day (bis in die)
CNS	Central Nervous System
EOS	End of Study
EOT	End of Treatment
GE	Gastroenterologist
GP	General Practitioner
H. pylori	*Helicobacter pylori*
HCl	Hydrochloric Acid
MALT	Mucosa-Associated Lymphoid Tissue
PPI	Proton Pump Inhibitor
QID	Four Times a Day (quater in die)
SSC	Steady State Concentration
TMB	Trimethylbismuth
UBT	Urea Breath Test

1 INTRODUCTION

1.1 BACKGROUND

Though nearly 25 years have passed since *Helicobacter pylori (H. pylori)* was first associated with gastritis and peptic ulceration[1], *H. pylori* continues to be a pathogen eliciting significant clinical burden to those infected, including gastric carcinoma[2-4] and mucosa associated lymphoid tissue (MALT)[5-9].

Both the European[10] and American[11,12] Guidelines recommend the "test-and-treat" approach in subjects presenting in primary care with chronic and recurrent dyspepsia without alarm features. Many antibacterial treatments have been tested for the eradication of *H. pylori*, including bismuth-based therapies (bismuth, metronidazole, and tetracycline hydrochloride). The increasing resistance of *H. pylori* to metronidazole has led to improvements to bismuth-based therapies, primarily with the addition of a proton pump inhibitor (PPI) to form quadruple therapy. Clinical evidence has indicated that PPI-supplemented bismuth-based regimens result in decreased pain and an improved bacterial eradication rate, even in metronidazole resistant strains of *H. pylori*[13,14,15].

Aptalis Pharma US, Inc. developed Pylera®, an innovative capsule-based therapy containing 140 mg bismuth subcitrate potassium (as 40 mg Bi_2O_3), 125 mg metronidazole, and 125 mg tetracycline hydrochloride (HCl), to be administered as 3 capsules four times a day (QID) for 10 days with omeprazole.

Two multicenter, Phase III efficacy and safety trials were conducted using Pylera® plus omeprazole over a 10-day course of treatment, which resulted in the approval of Pylera® by the United States Food and Drug Administration (FDA) on 29 September 2006 and subsequent launch in the United States in May 2007[16]:

- The first study evaluated the eradication rate of Pylera® plus omeprazole in *H. pylori* positive subjects with symptoms of dyspepsia either with or without a history of peptic ulcers. The eradication rate was 93%. There was no significant difference in eradication in subjects with and without a history of peptic ulcers[17].
- The second study compared Pylera® plus omeprazole to a clarithromycin-base triple therapy (omeprazole, amoxicillin, clarithromycin; OAC) given for 10 days in *H. pylori* positive subjects with symptoms of dyspepsia, but who had either active ulcer(s) or a history of peptic ulcers. The results indicated that the eradication rates were similar for both groups, with eradication rates of 87.7% with Pylera® plus omeprazole treatment versus vs. 83.2% with OAC treatment. Pylera® plus omeprazole eradication rates were 91.7% for metronidazole-sensitive strains and 80.4% for metronidazole-resistant strains. Triple therapy with OAC demonstrated eradication rates of 92.1% in clarithromycin-sensitive strains and 21.4% in clarithromycin-resistant strains[18].

A third Phase III clinical trial conducted in seven European countries formed the basis for the Marketing Authorisation Application (MAA) that recently completed decentralized assessment in nine European Union (EU) countries. This study compared Pylera® plus omeprazole given as a 10-day treatment course to OAC given as a 7-day treatment course, which is the current standard of care in Europe. Study results established the superiority of Pylera® plus omeprazole over OAC, with a 23.4% difference in eradication rates of *H. pylori* (93.3% for Pylera® plus omeprazole versus 69.6% for OAC; $p < 0.001$)[19].

During review of the MAA, one major concern pertaining to the full PK profile of bismuth was raised. Bismuth-associated encephalopathies associated with the clinical use of other forms of bismuth salts were reported in the 1970s[20,21]. Nephrotoxicity has also been reported with bismuth subsalicylate and the heptadiene carboxylic acid salt of bismuth[22]. These toxicities have historically been associated with prolonged daily intake (sometimes measuring years in length) of large quantities of bismuth (up to 21 g/day)[20,23].

Although absorption of bismuth subcitrate potassium (the bismuth salt found in Pylera®) was found to be negligible during the product's development cycle[24,25], a Phase I study was conducted in *H. pylori*-infected subjects to document blood plasma and whole blood bismuth bioavailability under the full mode administration of Pylera® (10-day treatment period with medication intake with food). This study enrolled 32 subjects, well above the 24 subject minimum requested to account for the high variability of bismuth concentrations between subjects. The PK profile of bismuth in blood and plasma following 10-day QID dosing of Pylera® with omeprazole BID did not raise safety concerns regarding any risk of central neurotoxicity related to bismuth up to 28 days post-final dose[26].

Plasma and blood bismuth concentrations were similar, with steady state concentrations (SSC) attained by Day 4. All subjects had Day 10 average SSC below the Hillemand *et al*. (1977)[27] alert value of 50 µg/L bismuth. The chronic bismuth concentrations published by Hillemand *et al*. are generally accepted safety levels for which a physician must be alert to the possibility of encephalopathies ("alert value": >50 µg/L sustained bismuth concentration) and to which a physician must act ("panic value": >100 µg/L sustained bismuth concentration). Based on this proposal, sustained steady-state blood levels of bismuth lower than 50 µg/L should not be associated with severe (intensity) bismuth-related Adverse Events.

The complete population view of bismuth from this PK study showed high variability of bismuth concentration among the different subjects and samples. Nevertheless, certain trends were apparent. Samples from Days 1-9 (hours 0 → 208), drawn towards the end of the dosing interval of the first dosage of the day, reflected a low level of bismuth as the peak absorption levels which were not reflected in the sampling scheme. The average 24-hour trough plasma level (4.66 µg/L) reflected rapid distribution, and there were no sustained levels with any subject at any time above approximately 20 µg/L.

As the sampling frequency was increased during the intensive sampling phase of this study, peak plasma levels are more clearly defined. These peak plasma levels typically occurred within one hour after administration of the dose, and represented the very small fraction of administered drug that managed to reach the blood from the dose. This small fraction was rapidly distributed to the tissues (a small amount is believed to be excreted in the urine) and the peak plasma level quickly declined.

Peak plasma concentrations >50 µg/L were sporadically seen in 12/28 subjects; 8/28 had similar sporadic blood concentrations. Transient plasma and blood concentrations >100 µg/L were noted in 2/28 and 1/28 subjects respectively. Levels were elevated for less than one hour on each occasion. There is no evidence to suggest that such peaks are toxic, even with levels above 100 µg/L[28].

For central nervous system disorders, only headache was considered possibly related to study drug. 7/32 (22%) subjects experienced 10 episodes of headache. 4/7 subjects had Day 10 plasma bismuth SSC >50 µg/L, 3 also had blood bismuth Cmax >50 µg/L. These 4 had 7 episodes of headache, with 2 having more than 1 episode (2 or 3 episodes). The remaining 3 subjects had Day 10 plasma and blood bismuth Cmax <50 µg/L and reported 3 episodes of headache. None of these adverse events were suggestive of a potential central neurotoxicity of bismuth, especially considering that multiple component of the study drug are liable to induce headaches.

An expert neurology report further concluded that central nervous system symptoms attributable to bismuth are highly unlikely when the indicated 10-day treatment course is utilized[29].

1.2 RATIONALE FOR THE STUDY

As part of the Pylera® MAA, a post-marketing PK program to be conducted in France was requested to observe potential changes in bismuth concentrations arising from real-life use of Pylera® in the general population, including poor compliance, misuse, or the concomitant use of other medications.

The present study is designed to address this request.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To verify the absence of accumulation of bismuth in subjects prescribed Pylera®, a pharmacokinetic approach in a real-life setting.

2.2 SECONDARY OBJECTIVES

1. To evaluate treatment effectiveness by the eradication measured by a negative diagnostic *H. pylori* test (breath test, biopsy, or other test at the discretion of the Investigator) for subjects with an initially positive *H. pylori* test.
2. To compare post-treatment bismuth concentrations in treatment successes and failures.
3. To evaluate the accumulation of bismuth in subjects receiving Pylera® with omeprazole *versus* subjects who may have received Pylera® with another proton pump inhibitor (PPI) other than omeprazole.
4. To compare population safety data profiles in treatment successes and failures.

2.3 SAFETY AND EFFICACY VARIABLES

2.3.1 Safety Variables

The safety profile will be assessed in terms of overall AEs, vital signs, and concomitant medication usage over the 10-day treatment period, as well as at the 4 weeks follow-up period after treatment.

There will be an additional follow-up for neurological adverse events (AEs) indicative of encephalopathy.

2.3.2 Efficacy Variables

A post-treatment diagnostic result of *H. pylori* test for eradication (e.g. breath test, biopsy, or other test) at the discretion of the Investigator.

3 STUDY DESCRIPTION (STUDY DESIGN)

3.1 OVERALL STUDY DESCRIPTION

This study is a multicenter, open-label, single-arm, clinical trial to be conducted exclusively in France and involving two hundred (200) eligible subjects. A detailed description of study procedures and study conduct is presented in Section 9 and Appendix 1 of this protocol.

The study will consist of an Investigator pre-selection period, and a subject treatment period.

The Investigator pre-selection period will identify likely prescriber profiles within a national reimbursement database (e.g., the EGB representative sample in France), or other applicable databases to determine the distribution of Gastroenterologists (GE) and General Practitioners (GP) based on appropriate measures including but not limited to the prescription of UBT or other diagnostic tests for *H. pylori*, or the prescription patterns of Pylera® when it is marketed.

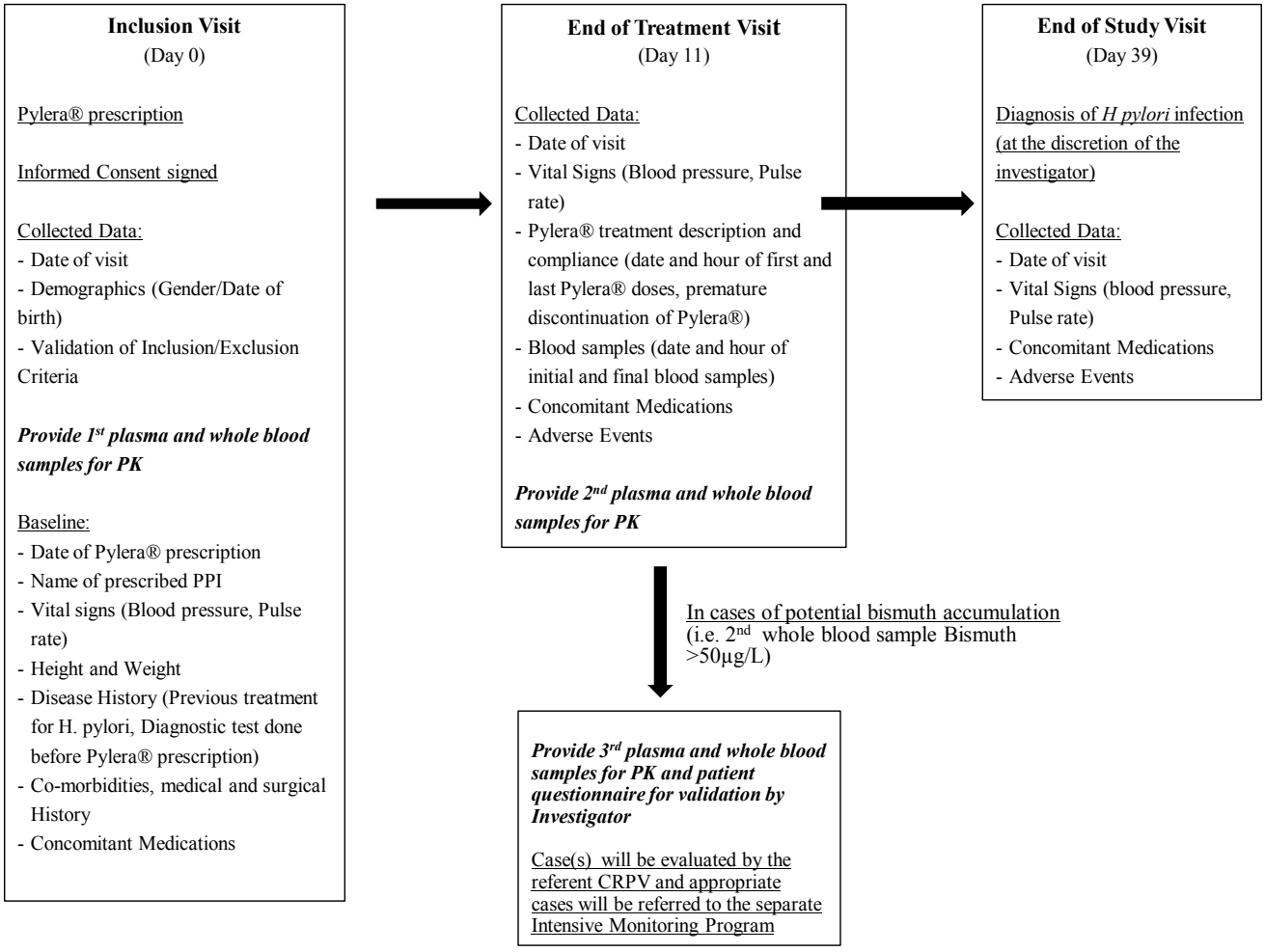
This pre-selection analysis will also identify usage patterns per prescriber in order to evaluate the number of prescribers required to accrue the expected number of subjects without seeding.

Following identification of the GE/GP ratio and the calculation of sites required to complete recruitment within the 24 month timeframe, specific databases of health professionals such as CEGEDIM will be used to contact GPs and/or GEs to propose participation in the study as per the GE/GP prescriber ratio described above.

The subject study period will be conducted at these participating sites and will be comprised of three steps as follows:

1. Inclusion Visit (Day 0)
2. End of Treatment Period (EOT) Visit (Day 11)
3. End of Study (EOS) Visit (Day 39)

An allowance for participation will be provided to each patient at the end of the 3rd visit.


Inclusion Visit
(Day 0)
Pylera® prescription
Informed Consent signed
Collected Data:
- Date of visit
- Demographics (Gender/Date of birth)
- Validation of Inclusion/Exclusion Criteria
Provide 1st plasma and whole blood samples for PK
Baseline:
- Date of Pylera® prescription
- Name of prescribed PPI
- Vital signs (Blood pressure, Pulse rate)
- Height and Weight
- Disease History (Previous treatment for H. pylori, Diagnostic test done before Pylera® prescription)
- Co-morbidities, medical and surgical History
- Concomitant Medications
End of Treatment Visit
(Day 11)
Collected Data:
- Date of visit
- Vital Signs (Blood pressure, Pulse rate)
- Pylera® treatment description and compliance (date and hour of first and last Pylera® doses, premature discontinuation of Pylera®)
- Blood samples (date and hour of initial and final blood samples)
- Concomitant Medications
- Adverse Events
Provide 2nd plasma and whole blood samples for PK
In cases of potential bismuth accumulation (i.e. 2nd whole blood sample Bismuth >50µg/L)
Provide 3rd plasma and whole blood samples for PK and patient questionnaire for validation by Investigator
Case(s) will be evaluated by the referent CRPV and appropriate cases will be referred to the separate Intensive Monitoring Program
End of Study Visit
(Day 39)
Diagnosis of H pylori infection (at the discretion of the investigator)
Collected Data:
- Date of visit
- Vital Signs (blood pressure, Pulse rate)
- Concomitant Medications
- Adverse Events

3.2 SCHEDULING OF VISITS

Patient inclusion in the study will be considered after the decision to treat with Pylera® has been made by the Investigator.

The Inclusion Visit will be initiated following signature of Informed Consent.

Information regarding date of Pylera® prescription, name of prescribed PPI, demographic data, vital signs, height, weight, disease history for *H. pylori* infection (including information pertaining to prior *H. pylori* treatment), co-morbidities, medical and surgical history — will be surveyed, as well as information concerning diagnostic procedures performed to verify *H. pylori* infection.

Upon confirmation of eligibility, subjects will be given instructions for the first blood sample (D0 sample) for bismuth and TMB PK prior to initiating treatment with Pylera®, and an appointment for the second blood sampling.

Upon completion of the 10-day treatment with Pylera®, subjects will proceed to the EOT Visit to provide the second blood sample (D11 sample) for bismuth and TMB PK.

Subjects who demonstrate clinical symptoms indicative of bismuth-related neurological adverse events or bismuth accumulation at the EOT Visit (total bismuth in whole blood> 50 μg/L) will be requested to return to the laboratory immediately to draw a third blood sample for evaluation of bismuth. Subjects having clinical symptoms indicative of bismuth-related neurological adverse events will be referred to the separate Intensive Monitoring Program. If bismuth concentration remains sustained in subjects with no neurological symptoms and subject interview with Investigator confirms that no third-party source of bismuth was consumed outside of the context of this study, the subject will be referred to the separate Intensive Monitoring Program to be evaluated for inclusion.

A diagnostic *H. pylori* test (breath test, biopsy, or other test at the discretion of the Investigator) to assess *H. pylori* eradication should be repeated on one single occasion at least 28 days post-treatment as part of the EOS Visit.

Vital signs, concomitant medications, adverse events (AEs) and the presence of central nervous system (CNS) adverse events of interest as listed in Appendix 3 will be assessed at the EOT and EOS Visits.

3.3 ESTIMATED DURATION OF THE STUDY

This study has an anticipated recruitment period of 24 months, with the recruitment Initiation Date (First Subject, First Visit) expected to be within 6 calendar months of the launch of Pylera® marketing activities in France.

The recruitment Completion Date (Last Subject, First Visit) is expected to occur 24 months following study start (approximately 30 calendar months from marketing launch). Inclusion rates will depend on the drug's uptake within the French market. It is estimated the total study duration will not exceed 3 years. Actual duration will be shorter if feasible, but is very much dependent on market penetration of Pylera® in France.

Eligible subjects will stay in study for approximately 6 weeks.

4 STUDY POPULATION

4.1 NUMBER OF SUBJECTS

As per requirement by the regulatory authorities, 200 eligible men and women 18 year of age and older will be recruited into the study.

4.2 SELECTION CRITERIA

4.2.1 Inclusion Criteria

To be eligible, subjects must meet all of the following criteria:

#	Inclusion Criteria Description
1	Men and women 18 years of age and older who have received a prescription for Pylera® therapy from the Investigator
2	Mental and legal ability to give written Informed Consent and judged by the Investigator to be capable of following the procedures outlined within the protocol

4.2.2 Exclusion Criteria

Subjects with any of the following conditions must be excluded from this study.

#	Exclusion Criteria Description
1	Women who are pregnant or nursing
2	Any concern by the Investigator regarding the safe participation of the subject in the study or for any other reason the Investigator considers the subject inappropriate for participation in the study

4.3 CONCOMITANT MEDICATION

4.3.1 Previous and Concomitant Medication

The brand name (or if unknown, the generic name), dose unit (or dosage form if a compound medication), frequency, start date and, if applicable, stop date for all previous medications (taken 3 months prior to Informed Consent Form [ICF] signature) and concomitant medications (taken at the time of the ICF signature and during the course of the study) must be documented in the Case Report Form (CRF). Medications include prescription medications, intravenous fluids, herbals, vitamins, and any other over-the-counter medicines.

4.3.2 Prohibited Medication

It is expected that subjects will have already been appropriately screened by the Investigator as per information listed in the "Interaction with other medicinal products and other forms of interaction" section of the Pylera® SmPC.

4.4 ADJUNCTIVE THERAPY / PROCEDURE

Not applicable.

4.5 ACCEPTABLE CONTRACEPTIVE REGIMEN

Pylera® capsules of bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride given with omeprazole are considered contraindicated for use during pregnancy. Nevertheless, current regulations and guidelines pertaining to pharmaceutical industry require properly documenting and monitoring exposure to any investigational or marketed drugs under clinical research during pregnancy of study female subjects and the partner of study male subjects.

It is expected that women of childbearing potential will have already been appropriately screened by the Investigator as per the "Pregnancy and lactation" section of the Pylera® SmPC and that such individuals who are not pregnant and not nursing will take appropriate measures to prevent pregnancy while using Pylera®.

Women who are pregnant or nursing are excluded from participation in this study.

4.6 DISCONTINUATION CRITERIA

A subject has the right to withdraw from the study at any time for any reason without penalty or prejudice. The Investigator also has the right to withdraw a subject from the study if he/she feels it is in the best interest of the subject or if the subject is uncooperative or noncompliant. Should a subject decide to withdraw, all efforts will be made to complete and report the observations and early withdrawal procedures as thoroughly as possible.

Subjects who withdraw subsequent to the signing consent but before receiving the prescription for Pylera® will be considered "screening failures" and will be replaced to ensure that 200 evaluable subjects complete the study.

Discontinuation may occur because of any one of the following reasons among others:

#	Discontinuation criteria
1	The subject has been included in violation of the inclusion / exclusion criteria

2	The subject chooses to discontinue participation for personal reasons (moving away, no time, etc.)
3	The subject chooses to discontinue, or is discontinued by the Investigator or the sponsor, due to an AE
4	The Investigator or the sponsor discontinues the subject for a significant protocol deviation
5	A newly developed illness, as determined by the physician in charge, that compromises continued participation
6	The subject uses a prohibited medication during the study (as described under Section 4.3.2)
7	In the Investigator or sponsor's judgment, withdrawal from the study would be in the subject's best interest (e.g., an immediate medical or surgical procedure is required that would compromise the subject's continued participation, lack of adequate therapeutic response resulting in intolerable symptoms or unacceptable risk)
8	The subject is uncooperative or does not comply with the protocol requirements (e.g., failure to return for scheduled visits at the enrolling study site, failure to complete study evaluation, etc.)
9	The sponsor terminates the study

For any subject who leaves the study, the Investigator must complete the CRF up to the time of withdrawal, ascertain the reason for discontinuation, and perform the EOS procedures. All reasonable efforts must be made to contact subjects who fail to return for scheduled visits and to encourage them to comply with the procedure. All attempts to contact subjects either by phone, courier, and/or email must be clearly documented. In case of withdrawal of consent, the date of withdrawal and the reason for withdrawing consent if provided by the subject will be collected. No additional data will be collected from the time of withdrawal of consent.

In the case of premature voluntary withdrawal of a subject with the premature stop of treatment with Pylera®, the subject will be excluded from the study and will be monitored separately. For subjects who have halted treatment with Pylera® and have withdrawn due to a neurological AE indicative of bismuth encephalopathy, the subject will be followed up through a separate Pylera® Intensive Monitoring Program.

5 STRATIFICATION AND RANDOMIZATION

As this is a single arm open-label study, no randomization will occur. No *a priori* stratification of subjects will be performed for this study.

6 UNBLINDING

Not applicable.

7 ADMINISTRATIVE PROCEDURES AND ETHICAL CONSIDERATIONS

Aptalis Pharma US, Inc. ensures the following obligations and administrative aspects of the study have been discussed with Investigators. These are described below:

- The Investigator must acknowledge Aptalis Pharma US, Inc. has instituted a Quality Assurance program according to Good Clinical Practices (GCPs), International Conference on Harmonisation (ICH) Guidelines and applicable laws and regulations;
- The Investigator must agree to allow study monitoring activities throughout the conduct of the study;
- The Investigator must agree to the inspection of study-related records by regulatory agency and/or Aptalis Pharma US, Inc. or designate;
- The Investigator must adhere to the European Medicines Agency (EMA) principles in addition to any applicable or local requirements.
- The Investigator must document in the CRF, Pylera® treatment description and compliance: date of first dose, date and hour of last dose, premature discontinuation of Pylera®, and if the subject took all doses.

7.1 AUDITING PROCEDURES

Aptalis Pharma US, Inc. has instituted a Quality Assurance program to ensure all aspects of the study have been conducted according to Good Clinical Practices, ICH Guidelines and applicable laws and regulations. This may include but is not limited to an audit by Aptalis Pharma US, Inc. and/or regulatory agency representative (Health Protection and Food Branch at Health Canada, Food and Drug Administration [FDA] of United States of America, EMA of European Union, and any other health regulatory agencies) at any time. The Investigator must agree to the audit of study-related records by regulatory agency and/or Aptalis Pharma US, Inc. The Investigator must adhere to the following principles, in addition to any applicable or local requirements.

7.2 MEDICAL CARE

Subjects will be informed that their medical care will not be affected by their agreement or refusal to participate in this study, and that they are free to withdraw from the study at any time without prejudice to the clinician-subject relationship.

7.3 SUBJECT INFORMATION AND INFORMED CONSENT

Information will be provided to explain, in simple terms, the risks and benefits of the subject's participation in the study, the procedures involved, and other relevant details. Written Informed Consent must be obtained from the subject by the Investigator before the subject enters the study.

The Investigator must adopt a standardized approach for obtaining Informed Consent from each subject. The following items must be described fully to each subject prior to obtaining consent:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed and identification of any procedures which are experimental;
- A description of any reasonable foreseeable risks or discomforts to the subject;
- A description of any benefits to the subject, which may reasonably be expected from the research;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the sponsor and the worldwide regulatory agency will inspect the records;
- An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject;
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;
- A statement that participation in the bio collection is voluntary and that the subject may request the destruction of his/her biological samples;
- Anticipated circumstance under which the subject's participation may be terminated by the Investigator without regard to the subject's consent;
- Any additional costs to the subject that may result from participation in the research;
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject;
- The approximate number of subjects involved in the study; and
- Any other country-specific and ICH/GCP requirements.

Should the Investigator decide to modify the Informed Consent document, the modified version must be approved by Aptalis Pharma US, Inc. prior to its submission to the Research Ethics Board (REB)/ Institutional Review Board (IRB)/ Independent Ethics Committee (IEC). Should the REB/IRB/IEC request modifications; the REB/IRB/IEC's version must be submitted to Aptalis Pharma US, Inc. prior to study initiation.

The original signed Informed Consent document should be maintained with the source documents. The subject should receive a copy of the signed Informed Consent document. All signed and dated Informed Consent documents will be inspected by the Aptalis Pharma US, Inc. Clinical Research Associate (CRA).

7.4 ETHICS COMMITTEE REVIEW

The protocol and the Informed Consent document to be used in this study must be submitted to the Investigator's appropriate REB/IRB/IEC for approval. Written documentation of approval of the protocol, any protocol amendment(s) and the Informed Consent must be provided to the sponsor before starting the study. When necessary, an extension or renewal of the REB/IRB/IEC approval must be obtained and also forwarded to Aptalis Pharma US, Inc.

Upon approval and before study start, the following REB, IRB or IEC Approval Documentation must be sent to Aptalis Pharma US, Inc.:

- A letter documenting the REB, IRB or IEC approval of the protocol (indicating its title and number) and the Informed Consent document.
- A letter documenting the REB, IRB, or IEC approval of amendment(s) to the protocol (indicating its title and number) and/or the Informed Consent Form, if applicable.
- A list of the REB, IRB or IEC members, their representative capacity, and their affiliation.

The ICH Guidelines for GCP specify the committee should include persons of varying backgrounds (including peers of the responsible Investigator and lay people) and must exclude the responsible Investigator as a voting member.

7.5 STANDARDS

The study will be conducted according to the principles of the Declaration of Helsinki (Seoul, October 2008), and the ICH Guidelines for Good Clinical Practice. The Sponsor will ensure the study complies with all local, federal or country regulatory requirements as applicable.

7.6 CONFIDENTIALITY

Subjects will only be identified with a subject number. Their names will not be disclosed in any publication or presentation of results.

7.7 PROTOCOL ADHERENCE

Subjects who fail to adhere to protocol will be assessed on whether or not the lack of adherence was due to AEs.

The Investigator should make every effort to ensure that visits occur at the appropriate intervals. The reason for any deviation in the visit schedule must be documented in the CRF.

7.8 PROTOCOL AMENDMENTS AND OTHER CHANGES IN STUDY CONDUCT

Any substantial changes, other than strictly administrative changes that do not affect patient management, patient safety, clinical procedures, or outcomes assessment, will be made as formal amendments to the protocol and will be submitted to each participating site for appropriate review by an IRB, IEC, or a REB, and to regulatory authorities.

Any change or addition to this protocol requires a written protocol amendment that must be approved by Aptalis Pharma US, Inc. and the Investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study, require additional approval by the IRB/IEC/REB of all centers, and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC/REB, which becomes part of the protocol, must be given to the Aptalis Pharma US, Inc. CRA.

These are examples of amendments requiring such approval:

- Any increase in drug dosage or duration of exposure of human subjects to the drug beyond that in the current protocol;
- Any significant increase in the number of human subjects under study;
- Any significant change in the design of the protocol (such as the addition or dropping of a control group);
- Addition or deletion of a test procedure for safety monitoring
- An increase in the number of invasive procedures to which subjects are exposed

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by Aptalis Pharma US, Inc. in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons Aptalis Pharma US, Inc. should be notified and the IRB/IEC/REB at the center should be informed within 10 working days. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes.

An example of an administrative change not requiring formal protocol amendments and IRB/IEC/REB approval that can be treated as administrative amendments is as follows:

- Changes in the staff used to monitor trials (e.g., Aptalis Pharma US, Inc. staff versus Academic Research Organization (ARO) staff)

Changes in study conduct as defined in this protocol are not permitted. Any planned deviation from the specific requirements of the protocol must be discussed in advance with Aptalis Pharma US, Inc. and will require prior approval. Any unforeseen changes in study conduct will be recorded in the clinical study report. Please see section 11.6 for additional information on protocol deviations.

8 MATERIALS AND STUDY DRUG

Not applicable.

This study is designed to capture pharmacokinetics information on bismuth and TMB in a naturalistic real-world setting. No study medication *per se* will be distributed during the course of this study. The patient will be instructed to take the Pylera® as prescribed by the Investigator.

9 STUDY PROCEDURES

The study procedures pertaining to the conduct of the study and as well as a detailed description of study procedures to be performed are summarized in Appendix 1 (Study Flowchart).

9.1 INCLUSION PROCEDURES

9.1.1 Informed Consent / Instructions to subjects

Before a subject is enrolled in this study and prior to the performance of any evaluations or study procedures, the Investigator or designee must explain the study to the subject in sufficient detail to allow for her/his informed decision to participate. The Investigator must adopt a standardized approach for obtaining Informed Consent from each subject. Availability of alternative treatment must be fully explained to the subject and documented in the Informed Consent Form (ICF). If the subject understands the requirements of the study and agrees to participate, the subject will sign the ICF. This form must also be signed by the Investigator or designee. All signatures must be dated. If the Investigator chooses to alter a medical regimen of the subject for the purpose of enrolling the subject in this study, the Informed Consent for the study should be signed at that time and prior to any alteration in the subject's ongoing therapeutic regimen. A copy of the signed and dated consent form must be given to the subject before the subject initiates the study. The signed ICF must be available for an Aptalis Pharma US, Inc. CRA or designee for on-site review. Upon willingness to participate in the study, each subject will be enrolled in the study by assignment of a unique sequential enrollment number for each study site.

9.1.2 Observations and Measurements

Following the granting of Informed Consent, each subject will be assigned a subject number in sequential order.

The following Inclusion Visit procedures and evaluations in addition to procedures normally conducted as part of standard of care will be performed after Informed Consent will be recorded in the appropriate sections of the CRF:

- Demographic data
- Confirmation of inclusion and exclusion criteria
- Date of Pylera® prescription
- Name of prescribed PPI
- Vital signs measurement (blood pressure, pulse rate), height and weight
- Disease history regarding *H. pylori* infection with previous *H. pylori* treatment and diagnostic tests with date and results (negative/positive)
- Co-morbidities, medical/surgical history
- Recording of prior and concomitant medications

Subjects will provide one blood sample as the baseline sample (D0 sample) for assessment of plasma and whole blood bismuth concentrations and whole blood trimethylbismuth (TMB) concentrations as per the procedures outlined in Appendix 2.

Once the D0 sampling is complete, subjects will be given an appointment for the second blood sampling (D11 sample) and subjects may initiate treatment with Pylera®.

9.1.3 Randomization Procedures

There is no randomization procedure as this is an open-label, single-arm study.

9.2 DURING TREATMENT PROCEDURES

- Recording of AEs in case a patient contact the Investigator

9.2.1 Subjects who completed treatment with Pylera®

Subjects who have completed the 10-day treatment with Pylera® will return to complete the following procedures as part of the EOT Visit:

- Vital signs measurement (blood pressure, pulse rate)
- Recording Pylera® treatment description and compliance
- Recording of concomitant medications
- Recording of AEs

The presence of CNS adverse events of specific interest as listed in Appendix 3 will be assessed at this visit with the specific form "Pharmacovigilance reporting form-neurological disorders and bismuth" developed for the collection of the adverse events of special interest as part of the Intensive Monitoring Program that will be completed by the Investigator.

Subjects will provide one blood sample as the post-treatment sample (D11 sample) for assessment of plasma and whole blood bismuth concentrations as well as whole blood TMB concentrations as per the procedures outlined in Appendix 2.

Subjects who demonstrate bismuth accumulation in whole blood at the EOT Visit (> 50 µg/L) will be requested to return immediately to the laboratory to draw a third blood sample for evaluation of bismuth. If bismuth concentration remains sustained and subject interview with Investigator confirms that no third-party source of bismuth was consumed outside of the context

of this study, the subject will be referred to the separate Intensive Monitoring Program to be evaluated for inclusion.

Subjects will return 28 days after the EOT Visit to complete the EOS Visit. At this visit, subjects will complete:

- Vital signs measurement (blood pressure, pulse rate)
- Recording eradication test
- Recording of concomitant medications
- Recording of AEs

The presence of CNS adverse events of specific interest as listed in Appendix 3 will be assessed at this visit with the specific form "Pharmacovigilance reporting form-neurological disorders and bismuth" developed for the collection of the adverse events of special interest as part of the Intensive Monitoring Program that will be completed by the Investigator.

Subjects who demonstrate a positive diagnostic *H. pylori* test (breath test, biopsy, or other test at the discretion of the Investigator) at End of Study will be documented by the completion of a specific form entitled "Targeted follow-up form – Pylera® eradication therapy failure". These subjects will be referred to treatment for *H. pylori* infection outside of the context of this study.

9.2.2 Subjects who prematurely discontinue treatment with Pylera®

For any subject who prematurely discontinues treatment with Pylera®, the Investigator will perform the EOS procedures and will complete appropriate pages of the CRF. A diagnostic *H. pylori* test (breath test, biopsy, or other test) will be conducted at the discretion of the Investigator.

In case of withdrawal of consent, only the date of and the reason for withdrawing consent will be collected on the CRF. Otherwise, the Investigator will make all reasonable effort to complete as much as possible the following at the time of discontinuation.

#	**Information to be collected**
1	Vital sign measurements (pulse rate, blood pressure measured from the same arm throughout the study)
2	Record of any occurrence of AEs, change in concurrent medical conditions, use of adjunctive therapy/procedure, and intake of concomitant medication
3	Collect safety information via a phone call to the patient 30 ± 5 days after discontinuation (includes AEs, change in concurrent medical conditions, use of adjunctive therapy/procedures, and intake of concomitant medication).

4	A diagnostic *H. pylori* test (breath test, biopsy, or other test) at the discretion of the Investigator

All results of evaluation and observations, together with the reason for withdrawal from the study, will be recorded on the CRF.

For any subject who prematurely discontinues treatment with Pylera® due to a neurological AE indicative of bismuth encephalopathy, the subject will be followed up through a separate Pylera® Intensive Monitoring Program.

9.3 CLINICAL LABORATORY PROCEDURES

Not applicable.

9.4 OTHER PROCEDURES

A diagnostic *H. pylori* test (breath test, biopsy, or other test at the discretion of the Investigator)

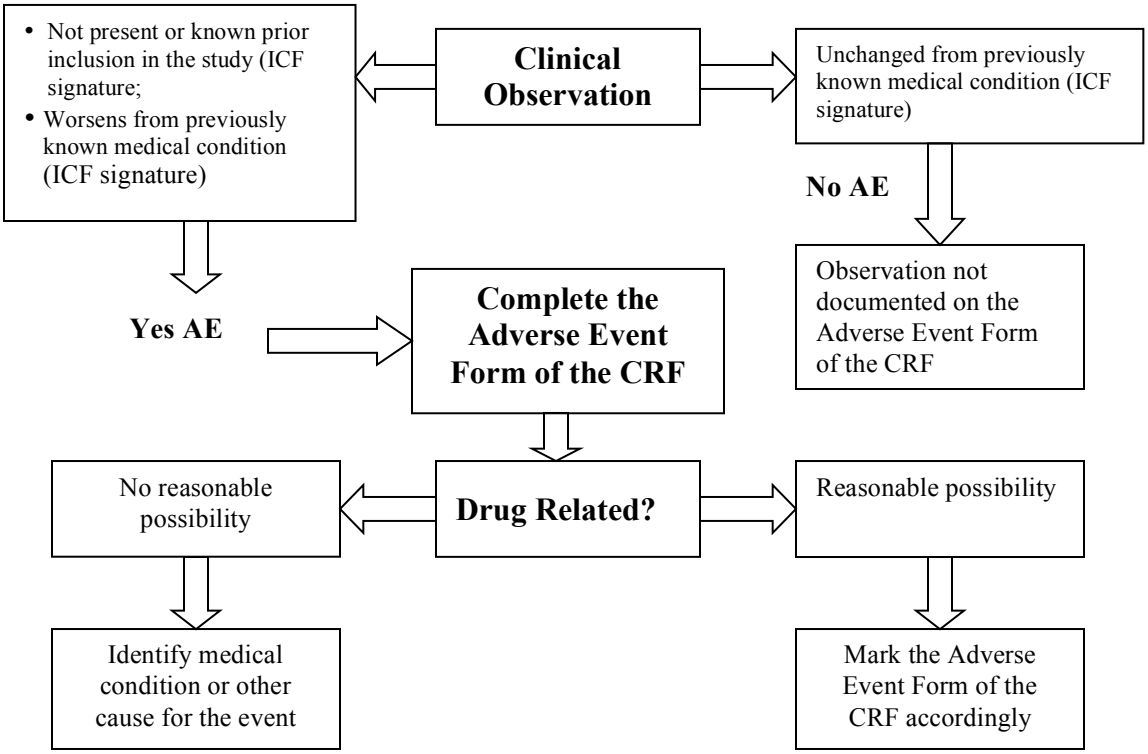
Presence of *H. pylori* will be assessed at the EOS Visit. The selection of the method for this assessment is at the discretion of the Investigator.

10 ADVERSE EVENTS

Subjects receiving any investigational drug require careful observation. Any adverse event/concurrent illness experienced by a subject during any portion of the study must be described in detail and be fully evaluated by the Investigator. The Investigator is responsible for recording all adverse events observed or reported during the study from Inform Consent signature until date of completion/discontinuation, regardless of the drug-related assessment and/or clinical significance. Any pertinent information must be recorded in the CRF and additional comments describing the course and outcome of these events should be provided as appropriate.

10.1 DEFINITIONS

An Adverse Event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject during the course of a clinical trial regardless of the causal relationship. The following flowchart illustrates the decision making process the Investigator should follow in determining how to document an AE in the study.



An **Unexpected Adverse Event** is defined as an adverse drug event, the nature or incidence of which is not consistent with applicable reference safety information (Pylera® SmPC [18 May 2012]; omeprazole Summary of Product Characteristics [February 2008]).

A **Serious Adverse Event (SAE)** is defined as any untoward medical occurrence that at any dose:

- Results in death; or
- Is life-threatening; or Requires inpatient hospitalization or prolongation of existing hospitalization excepting hospital admissions due to administrative reasons (e.g., the subject has no transportation home) or hospitalization for elective treatment of a pre-existing condition that did not worsen during the study unless a complication occurs during the hospitalization; or
- Results in permanent or significant disability/incapacity; or
- Results in congenital anomaly/birth defect.

Other important medical adverse events may also be considered serious, depending on the judgment of the Investigator or Aptalis Pharma US, Inc. (e.g., from ICH guidelines, intensive treatment in an emergency room or at home to prevent one of the outcomes listed in this

definition, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse).

Note that as defined, serious events (expected or not) are not necessarily causally associated with the study treatment.

In addition, suspected transmission of infectious agents should always be considered as a SAE.

10.2 PRE-EXISTING MEDICAL CONDITIONS

Any pre-existing medical conditions, which do not worsen in duration, intensity or frequency during the study are not considered to be AEs. These pre-existing medical conditions should be adequately documented in the medical history of the CRF and any other appropriate ancillary documents. Pre-existing medical conditions, which worsen after exposure to study treatment will be recorded as an AE on the Adverse Event Form of the CRF.

10.3 LABORATORY TEST ABNORMALITIES

During the course of the study, the Investigator will be required to comment on any laboratory values outside the normal reference range. A laboratory abnormality should be regarded as an AE and recorded on the Adverse Event Form of the CRF if, according to the Investigator's judgment, the value is significantly worse than at pretreatment and has been confirmed by repeat testing, when applicable. In addition, an abnormal laboratory test value discovered after ICF signature and that was not previously known should be considered as an AE.

10.4 GUIDELINES AND EVALUATION

To promote consistency between sites, the following guidelines should be taken into consideration along with good clinical judgment when documenting and recording AEs.

10.4.1 Assessment and Recording

An AE, whether or not considered causally related to the treatment, must be promptly documented and recorded. At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the appropriate open questions. In addition to straightforward subject observation (e.g., headache, nausea, etc.), AEs will also be documented from any data collected in the CRF (e.g., laboratory values, physical examination findings, etc.) or other documents (e.g., subject diaries) that are relevant to subject safety.

At each follow-up visit or assessment by phone or otherwise, all AEs, whether observed by the Investigator or one of his or her professional collaborators, or reported by the subject

spontaneously or in response to an open question, will be recorded in the Adverse Event Form included in the CRF with the following information.

- **Name of the AE**: Name should be a medical term. When possible, the Investigator should differentiate an illness entity from isolated symptoms or signs. For instance, the term "flu" should be recorded instead of listing all the flu-related symptoms. Where a differentiation is not possible, symptoms and signs should be separately recorded and evaluated as **Adverse Events.**
- **Start date and stop date (or statement that the event is continuing) of the AE**
- **Imputability of Pylera®:** evaluate the causal relationship between Pylera® and the AE as described in section 10.4.2
- **Seriousness criteria** as defined in section 10.1

The Aptalis Pharma US, Inc CRA who visits the center will check the completeness and accuracy of the Adverse Events Form. Wherever possible, all AEs regardless of the seriousness must be followed through resolution.

10.4.2 Causality Assessment

Part of the Adverse Event documentation will involve the Investigator making a causality assessment. To promote consistency between Investigators, the following guidelines should be taken into consideration along with good clinical judgment when determining the relationship of study medication to adverse event.

The following criteria can be used in order to evaluate the causal relationship between the study medication and the AE.

No reasonable possibility	☐ The AE is definitely not associated with the study treatment AND/OR ☐ The AE does not follow a reasonable temporal sequence from drug administration AND/OR ☐ The AE does not disappear or decrease on discontinuation of the study drug (dechallenge) and/or does not reappear or increase on repeated exposure (rechallenge) AND/OR ☐ The AE is reasonably explained by known characteristics of the patient's clinical state, history, environment, other therapy administered to the patient (drug or non-drug) AND/OR ☐ The AE may be caused by reasons other than administration of the study drug
Reasonable possibility	☐ The AE follows or may follow a reasonable temporal sequence from study treatment AND/OR ☐ The AE disappears or abates upon discontinuation of the study treatment (dechallenge) and/or reappears or increases on repeated exposure (rechallenge)

	AND/OR ☐ The AE cannot be reasonably explained by known characteristics of the patient's clinical state, history, environment, other therapy administered to the patient (drug or non-drug) AND/OR ☐ Previous experience with the study medication or related compounds resulted in a similar event AND/OR ☐ The AE is a known effect of the study treatment

10.4.3 Reporting Requirements

10.4.3.1 Serious Adverse Events

All SAEs, regardless of relationship to study treatment, must be reported by the Investigator to Aptalis Pharma US, Inc. by completing the SAE form of the CRF within 24 hours of awareness. This includes SAEs occurring as soon as the subject signs the Informed Consent (i.e. pre-treatment SAEs). The SAE form should be completed as thoroughly as possible, given the information available and time constraints. Upon completion, the SAE form should be signed by the Investigator or sub-Investigator using the CRF. SAEs which could be associated with the trial procedures and which could modify the conduct of the trial are reportable within 24 hours.

In addition, any spontaneously reported Serious Adverse Events (SAE: details in sections 10.1 and 10.5) that occurs within 30 days after the last study procedure or study drug administration should be recorded in the SAE form provided in the ISF.

The SAE Form should be completed as thoroughly as possible, given the information available and time constraints, signed and faxed or emailed to Aptalis Pharma US, Inc. (Drug Safety department, contact details provided within the ISF).

Email: **drugsafety@aptalispharma.com**

Death and surgery should not be reported as an event. Death and surgery are viewed as an outcome of an event, rather than the event itself. In cases where the cause of death is unknown, death may be initially reported as an event. Every attempt should be made to submit a follow-up report identifying the cause of death.

SAEs will be monitored by Aptalis Pharma US, Inc. in real time throughout the trial.

10.4.3.2 Adverse Events

All AEs will be reported on the Adverse Events Form of the CRF.

10.4.3.3 Other reportable events

The following events will be recorded and reported within 24 hours to Aptalis Pharma US, Inc. as described in Section 10.4.3.1:

- Any pregnancy that occurs in study subjects or their partners during the study should be recorded and reported to Aptalis Pharma US, Inc. using the appropriate Pregnancy Surveillance Form provided in the CRF. If a pregnancy occurs in a subject during the study, the administration of the investigational product must be discontinued. Follow-up should be ensured to collect information about the course of the pregnancy and delivery, as well as the condition of the newborn. When the newborn is healthy, additional follow-up is not needed. In case of health problem in the newborn, follow-up must be performed as described in section 10.5. The Investigator will provide follow-up information concerning the outcome of pregnancy to the sponsor in a timely manner.

- The following should be recorded and reported on the appropriate form provided in the CRF:

  - Drug abuse, misuse and overdose with or without AEs (an overdose is a dose higher than that prescribed by a health care professional for clinical reasons. It is up to the participating Investigator to decide whether a dose was an overdose).
  - Inadvertent or accidental exposure to the investigational product with or without an AE should be recorded and reported to Aptalis Pharma US, Inc.
  - Any other medication errors (including dispensing errors such as inadvertent use of expired medication and dosing errors) with or without an AE.
  - Suspected transmission of an infectious agent.

There will be additional follow-up for neurological adverse events indicative of encephalopathy through a separate and concomitant safety program, i.e. the Intensive Monitoring Program, as part of Risk management plan of Pylera. A "Pharmacovigilance reporting form – for neurological events with bismuth" shall be completed for each case where neurological symptoms listed in the Appendix 3, accompanied or not by bismuth whole blood concentrations above 50 µg/L occur. There will be a case review and confirmation by the Scientific Committee of the Intensive Monitoring Program for the diagnosis of encephalopathy. The assessment of the correlation between bismuth concentration and occurrence of neurological symptoms will be provided in the Periodic Safety Update Reports (PSUR) and in the reports from the Intensive Monitoring Program.

10.5 FOLLOW-UP AND FINAL REPORTS

The clinical condition of human subjects who have had a SAE must be followed until all parameters, including laboratory values, have either returned to normal or to baseline value or are

otherwise explained or judged acceptable by the Investigator. Follow up and/or Final Reports, including information on the action taken and the outcome, must be sent to Aptalis Pharma US, Inc.

In the event of death, any post-mortem findings (including histopathology, autopsy report) must be provided to Aptalis Pharma US, Inc.

If the follow-up information is received after the last study procedure or last study drug administration, this information will not be recorded in the CRF but should be provided to Aptalis Pharma US, Inc. using the Aptalis Pharma US, Inc. SAE form provided in the ISF.

10.6 REGULATORY ASPECTS

Aptalis Pharma US, Inc. has a legal responsibility to notify the HPFB of Canada, the FDA of the United States of America, the EMA, and the National Competent Authorities and Central Ethics Committees of European Union, and all other foreign regulatory agencies as well as all sites about the safety of the drug. The Investigator has the responsibility to notify the local Ethics Committee about SAEs.

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection(s), providing direct access to source data/documents. Copies of the notification to the ethics committee must be sent to Aptalis Pharma US, Inc.

10.7 DATA SAFETY MONITORING BOARD

No Data Safety Monitoring Board is planned for this study.

Subjects who demonstrate a neurologic AE indicative of bismuth toxicity, will be evaluated by the Scientific Committee of a separate Intensive Monitoring Program. Such neurologic AEs of interest will include but are not limited to disorders in walking, speech and writing with psychiatric symptoms including mental confusion and myoclonia, tremor, and lack of coordination.

Subjects who demonstrate bismuth accumulation at the End of Treatment Visit (> 50 μg/L) will be requested to immediately return to the laboratory to draw a third blood sample for evaluation of bismuth. If bismuth concentration remains sustained and subject interview with Investigator confirms that no third-party source of bismuth was consumed outside of the context of this study,

the subject will be referred to the separate Intensive Monitoring Program to be evaluated for inclusion.

The threshold for potential bismuth accumulation will be the Hillemand *et al*.[27] alert value of 50 µg/L, which will be defined as any accumulation value that is higher than 50 µg/L under the following formula:

Accumulation Value = (EOT bismuth concentration – Day 0 bismuth concentration)

11 DATA MANAGEMENT AND STATISTICS

11.1 SAMPLE SIZE/POWER CONSIDERATIONS

No sample size and power calculations have been conducted for this study as pharmacokinetic evaluations for two hundred (200) eligible subjects has been requested.

11.2 INTERIM ANALYSIS

An interim analysis of bismuth concentrations and study safety parameters is planned eighteen (18) months following the market launch of Pylera® in France, when 75 to 100 evaluable patients are expected to have been included in the study.

The analysis will be conducted to present the summary of the derived population PK parameters and the Confidence Interval. If low variability is found, the sponsor and the study project team will stop the study at 100 subjects, after consultation with Regulatory Agency.

11.3 SOURCE DOCUMENTS

All individual entries in source documentation require signature and date by the authors. All typed or dictated documents and computer printouts must be signed and dated by the Investigator to confirm review.

Preliminary laboratory reports including faxed copies must be initialed and dated and need to be retained. Final laboratory reports should be initialed and dated by the Investigator to confirm review. Original laboratory reports should be kept in file.

The following are considered to be source data:

- Medical charts, clinic charts, nurses' notes, medical correspondence regarding the human subject
- Subject progress notes
- Pathology reports
- Laboratory reports
- Study worksheets

Electronic (paperless) hospital reporting systems – the Investigator must sign and date a hard copy of this data for this to be considered a source document.

11.4 DATA COLLECTION AND CASE REPORT FORM MONITORING

All data will be collected using a paper-based multi-part Case Report Form (CRF).

The progress of the study will be monitored by telephone communication between site personnel and an Aptalis Pharma US, Inc designee. On-site visits will be performed at the end of the study to ensure compliance with the study protocol and to perform review of the subject CRF against the source document (subjects' medical record). On-site visits will also ensure that adequate records of clinical study supplies are maintained and to assess the continued suitability of the site.

11.5 DATA MANAGEMENT

A Data Management Plan and Data Review Plan will be developed to ensure the quality of the data.

11.5.1 Data Capture

Simplified data collection to characterize subject profile will be conducted using a paper-based multi-part CRF, which will capture:

- socio-demographic data, including age, sex, height, weight
- screening/baseline parameters prior to prescription of Pylera®, including medical history, vital signs, and results of a diagnostic *H. pylori* test (breath test, biopsy, or other test at the discretion of the Investigator) (if available), prescribed treatments, including:
  - Pylera® (indication, dose and duration of treatment)
  - PPI (indication, dose and duration of treatment)
  - other concomitant treatment(s)
- prior and concomitant medications
- AEs
- CNS AEs

A specific form will be completed by the subject and/or sampling laboratory to capture data related to PK blood draw. This form will capture subject characteristics, time of drug ingestion, time of sample, time elapsed since first drug intake, and time elapsed since last drug intake. This specific form will be completed at each blood draw and will be sent with each sample.

A specific form entitled "Targeted follow-up form – Pylera® eradication therapy failure" will be used to document subjects who demonstrate a positive diagnostic *H. pylori* test (breath test, biopsy, or other test at the discretion of the Investigator) infection at the EOS Visit. This form will permit a systematic assessment of the post-marketing case reports of lack of efficacy.

11.6 PROTOCOL DEVIATIONS

A protocol deviation is an unanticipated or unintentional divergence or departure from the expected conduct of the approved study that is not consistent with the current clinical protocol,

consent document or study addenda that could affect efficacy or safety parameters. Examples of protocol deviations include, but are not limited to, the following deviations:

- Enrolment of subjects outside protocol inclusion/exclusion criteria
- Changes in procedures initiated to eliminate immediate hazards to study subjects that could affect safety parameters
- Use of prohibited medication that could affect safety parameters
- Medically relevant omission of procedures
- Medically relevant sample loss
- Medication/intervention errors (e.g. incorrect study medication/intervention, incorrect dosage of the study medication)
- Significant change in the visit window or unapproved procedural deviation that could affect safety parameters
- Lack of subject adherence to study procedures
- Breach of confidentiality or privacy whereby confidential information about a subject is revealed in inappropriate settings, or to persons without a need to know, or by data exposure (computer security breach, documents left unsecured)
- Significant deviation from the consenting process (e.g. person who signed was not qualified, consent form was not signed)

All major protocol deviations must be reported on the Protocol Deviation Report Form provided and should be sent to the REB/IEC/IRB as per local policies.

In the case of a major protocol deviation, the Investigator will prospectively consult for appraisal, will fill out the appropriate section of the Protocol Deviation Report Form and will provide any supporting medical rationale/assessments. The sponsor will promptly evaluate all Protocol Deviation Report Forms and will document decision on subject management and follow-up instructions (if applicable) in the appropriate section of the form. A copy of the signed and dated form will be sent to the Investigator. Any major protocol deviation must obtain approval from the sponsor and from the Institution's IRB for the subject to enter or to remain in the trial.

In the event that an unreported major protocol deviation is discovered by the Investigator, the Protocol Deviation Report Form must be filled out immediately and sent to the sponsor for a retrospective appraisal.

In the case of minor protocol deviations, the Investigator should verify which ones need to be submitted to the REB/IEC/IRB as per local policies. Minor protocol deviations are not reported on the Protocol Deviation Report Form and will be reported on a comment page of the questionnaire.

11.7 DATA ANALYSIS

A detailed Statistical Analysis Plan (SAP) will be developed and filed before database lock.

Data from this study will be analyzed in a descriptive fashion. Summary tables will be produced at the interim analysis stage and after all 200 subjects have completed the study and following database lock.

11.7.1 Samples for analysis

11.7.1.1 Intent-to-treat Population

Not applicable.

11.7.1.2 Per Protocol Population

The Per Protocol (PP) population will consist of all subjects who have met the following criteria:

- have provided 1st and 2nd blood samples for plasma and whole blood PK data;
- have completed the study without any major protocol violations or other events considered to have potential impact to the full PK profile.

Major protocol deviations include all significant deviations to the protocol related to the inclusion/exclusion criteria, to the conduct of the trial, to the subject management or assessment of safety data and may include but not limited to the following:

- conduct of any study procedure prior to the signature of the ICF
- major deviation to study procedures
- premature withdrawal from study

11.7.1.3 Safety Population

The Safety Population will be defined as all enrolled subjects who have provided informed consent.

11.7.1.4 Definition of Type of Analysis

Analysis of safety variables will be based on the observed case analysis (no imputation at all).

11.7.2 Statistical Methodology

Descriptive statistics including the mean, median, standard deviation, minimum, and maximum will be presented for continuous variables. These statistical parameters, plus coefficient of variation and confidence intervals, will be used to describe bismuth plasma and whole blood

concentrations. For categorical variables, the number of subjects as well as the percentage within each category will be presented.

11.7.3 Analysis of Baseline and Demographic Data

Inclusion data with subject demographic information will be summarized using descriptive statistics for quantitative variables (e.g., weight, height, age) and counts and percentages for categorical variables (e.g., sex).

Additionally, subjects will be analyzed based on the method the decision to prescribe Pylera® was arrived at. This will include but not be limited to: Conduct of rapid urease test, conduct of UBT, and/or clinical evaluation.

11.7.4 Efficacy Analysis

11.7.4.1 Primary Efficacy Endpoint

Not applicable; this study is intended to assess the population PK of bismuth following treatment with Pylera®.

11.7.4.2 Secondary Efficacy Endpoints

The eradication rate of Pylera®, defined as the proportion of negative test of diagnostic *H. pylori* test (breath test, biopsy, or other test at the discretion of the Investigator) conducted at least 28 days following the end of treatment with Pylera®, will be calculated, including a 95% confidence interval. The eradication rates will be calculated for both the Safety and Per Protocol Populations.

11.7.5 Pooling of Investigative Sites

Not applicable.

11.7.6 Safety Analysis

Safety evaluations include vital signs, AEs and concomitant medications.

The safety profile will be assessed in terms of overall AEs, vital signs findings, and concomitant medication usage over the 10-day treatment period, as well as at the 4 weeks follow-up period after treatment.

Vital signs will be summarized descriptively. Change from baseline will also be summarized.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug dictionary. Medications initiated prior to start of study medication and maintained during

the study, or taken during the course of the trial will be considered as concomitant medications. Concomitant medications will be summarized according to the preferred terms.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects who experienced any AE as well as serious AE will be presented by system organ class and by preferred term within system organ class. All AEs will be similarly presented by seriousness criteria and by relationship to Pylera® (related/not related).

Safety analysis will be performed on the safety population for all subjects and for treatment successes and failures separately. No statistical comparisons will be performed.

There will be an additional follow-up for neurological adverse events indicative of encephalopathy through a separate and concomitant safety program, i.e. the Intensive Monitoring Program, as part of Risk management plan of Pylera®. A "Pharmacovigilance reporting form – for neurological events with bismuth" shall be completed for each case where neurological symptoms listed in the Appendix 3, accompanied or not by bismuth whole blood concentration above 50 µg/L occur. There will be a case review and confirmation by the Scientific Committee of the Intensive Monitoring Program for the diagnosis of encephalopathy. The assessment of the correlation between bismuth concentration and occurrence of neurological symptoms will be provided in the Periodic Safety Update Reports (PSUR) and in the reports from the Intensive Monitoring Program.

11.7.7 Pharmacokinetic / Pharmacodynamic Analysis

This study will focus on the detection and assessment of bismuth concentrations within the circulating plasma and whole blood compartment.

The initiation of any encephalopathy by an external compound requires the absorption of the material(s) and its transport to the central nervous system and its eventual crossing of the blood-brain-barrier; material which is not absorbed and eventually excreted in the feces will have no potential to induce an encephalopathy.

It is not known which metabolite(s) (if any) bismuth subcitrate potassium transforms to following ingestion of Pylera® by patients, and how such metabolites are further transformed. In the context of the clinical cases reported in the 1970s, it was never confirmed which bismuth metabolites generated the bismuth-associated encephalopathies.

One metabolite – trimethylbismuth (TMB) – is produced by methanoarchaea bacteria[31,32,33] present within the intestinal flora and is detectable at picogram levels within the circulating plasma compartment and by examination of respiratory exhalation[34]. TMB has been implicated in

bismuth-associated encephalopathies following the demonstration of encephalopathies in experimental animals exposed by inhalation to large uncontrolled quantities of TMB[35].

The detection of total bismuth (metal) rather than individual bismuth metabolites permits the detection of all bismuth circulating within the bloodstream irrespective of whatever metabolite form the bismuth atom is found in. Whole blood TMB will be evaluated using an analytical method derived from Boertz *et al*. (2009)[34] due to the possibility of encephalopathy arising from animal models. Post-treatment plasma and whole blood concentrations of bismuth (metal and TMB) will be described after subtraction of the baseline value for each subject using the following formula:

Accumulation Value = (EOT bismuth concentration – Day 0 bismuth concentration)

This comparison will include an evaluation of bismuth concentration in subjects who report neurological AEs and subjects who do not report neurological AEs.

After comparison on the whole sample, data will be stratified by the PPI used in combination with Pylera® and the comparison will be repeated in strata where sample size allows.

An additional comparison will be made of all post-treatment concentrations in the omeprazole group versus post-treatment concentrations of all other PPIs pooled together. For each subject the C_{min} will be grossly estimated assuming an elimination half-life of 19.95 hours[30] by the equation:

$$C_{\min} = \frac{C_{observed}}{e(-0.0347 * t)}$$

where *t* is the time elapsed between last dose intake and sampling time.

Individual observed results will also be classified as "above" or "below" the Hillemand *et al*.[27] alert threshold of 50 µg/L[27] for total whole blood bismuth concentrations solely as TMB has been calculated by Aptalis Pharma US, Inc. to exist at approximately 1:10,000 the level of average circulating bismuth concentrations.

For subjects who are already below 50 µg/L on Day 11, no other action will be performed and such subjects will be considered to have reached safe whole-blood levels within an acceptable time.

For subjects who are above 50 µg/L, the time required to reach 50 µg/L will be grossly estimated, again assuming an elimination half-life of 19.95 hours by the equation:

$$T_{recov} = \frac{ln\left(\frac{50}{C_{min}}\right)}{-0.0347}$$

Such subjects will also be referred for evaluation and potential inclusion in the separate Intensive Monitoring Program.

The number of subjects requiring more than 24 hours to reach safe levels and the time required will be considered to draw conclusion on the clinical safety of Pylera® with regard to bismuth toxicity.

11.7.8 Other

Not applicable.

12 DISCONTINUATION OF THE STUDY

Aptalis Pharma US, Inc. may terminate the study for safety, ethical or administrative reasons at any time. In such cases, all Investigators have to be notified immediately in writing, outlining the reasons for the termination. The Investigators will return the completed CRFs to Aptalis Pharma US, Inc.

In particular cases, the study may be terminated at a single investigational site, if the sponsor has relevant reasons (e.g., suspicion of fraud, lack of protocol compliance, lack of adherence to GCP, or no recruitment of subjects). In the case where a trial is discontinued, Aptalis Pharma US, Inc. will provide the Investigators with relevant procedures. Furthermore, the subject can withdraw from the study at any time without giving any reason.

Aptalis Pharma US, Inc. should promptly inform the regulatory authorities of all countries where the clinical study is being conducted (no later than 15 days in Canada and Europe) regarding the rationale for the termination of the study.

If the Investigator terminates his site participation in the study prematurely, the Investigator will provide a written statement as to why the study was terminated prematurely to Aptalis Pharma US, Inc.

The Investigator will complete a report notifying the REB/IRB/IEC of the conclusion of the clinical study. This report should be made within 15 days of completion or termination of the study. The final report sent to the REB/IRB/IEC will also be sent to Aptalis Pharma US, Inc. and, along with the completed CRFs, will constitute the final summary to Aptalis Pharma US, Inc. thereby fulfilling the Investigator's regulatory responsibility.

13 PUBLICATION POLICY

Aptalis Pharma designs and conducts clinical studies in an ethical and scientifically rigorous manner to determine the benefits, risks, and value of pharmaceutical products. Aptalis Pharma US, Inc is responsible for receipt and verification of data from all research sites for Aptalis Pharma US, Inc studies, to ensure the accuracy and integrity of the entire study database, which is owned by Aptalis Pharma US, Inc.

Aptalis Pharma US, Inc is committed to ensure that publication of all of its clinical studies results in biomedical journals are done in a timely manner, regardless of the study results. Publications should follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals (http://www.icmje.org). is committed to ensuring that authorship for all publications comply with the criteria defined by the ICMJE.

Clinical studies may involve already marketed products and/or investigational products. Aptalis Pharma US, Inc is committed to the timely submission and registration on a public database (e.g.Clintrials.gov) of summary information concerning relevant clinical studies that Aptalis Pharma US, Inc is conducting. These clinical studies will involve use of Aptalis Pharma US, Inc's marketed or investigational products. Aptalis Pharma US, Inc is also committed to the timely submission and posting of summary results of all clinical studies conducted in subjects involving the use of Aptalis Pharma US, Inc's products that are approved for marketing, or that are investigational products whose development programs are discontinued, regardless of outcome.

The publication rights of the investigators for this study are set forth in the individual agreements with each clinical sites.

14 INVESTIGATOR AGREEMENT

I have read the foregoing protocol "**A Safety and Pharmacokinetic study in Real-life practice of Pylera® in France: The SAPHARY Study**", and agree to conduct the study as described therein.

Investigator's name (block letters)

Investigator's signature

Date (dd/mmm/yyyy)

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16 APPENDICES

APPENDIX 1 – STUDY FLOWCHART

APPENDIX 2 – PHARMACOKINETICS BLOOD SAMPLING

APPENDIX 3 – CENTRAL NERVOUS SYSTEM ADVERSE EVENTS OF INTEREST

APPENDIX 1 - STUDY FLOWCHART

	Inclusion Visit (Day 0)	End of Visit (Day 11)	End of Study Visit (Day 39)
Informed Consent	X		
Demographics	X		
Inclusion/Exclusion criteria	X		
Vital Signs	X	X	X
Diagnostic tests done before Pylera® prescription[1]	X		
Co-morbidities, medical, surgical history	X		
Concomitant medications	X	X	X
Diagnostic *H. pylori* test (breath test, biopsy, or other test)	X		X[2]
Pharmacokinetics sample	X	X[3]	
Adverse events		X	X
CNS adverse events[4]		X	X

1. Including information pertaining to prior *H. pylori* treatment.
2. At the discretion of the Investigator
3. Subjects who demonstrate bismuth accumulation at the End of Treatment Visit (> 50 µg/L) will be referred to the separate Intensive Monitoring Program to be evaluated for inclusion. In case of inclusion, patients will be requested to return to the laboratory to draw a third blood sample for evaluation of bismuth). In case of neurological AE indicative of bismuth encephalopathy (please refer to Appendix 3 – Central Nervous System Adverse Events of Interest) if present at Day 11 blood samples will be as quickly processed as possible.
4. For CNS adverse event indicative of encephalopathy, follow-up will be perform by Intensive Monitoring Program

APPENDIX 2 – PHARMACOKINETICS BLOOD SAMPLING

The procedures described in this appendix detail the requirements for blood sampling and handling for pharmacokinetics samples.

Collection, processing, and transport will all be conducted with the samples shielded from light to minimize photo-degradation of any potential light-sensitive bismuth metabolite(s) within the samples.

1) Quantity collected and timeframe:
The total volume of blood drawn for bismuth and trimethylbismuth (TMB) pharmacokinetic assessment is anticipated to be 56 mL (8 x 7 mL tubes) over the full study period for each subject.

Blood samples will be drawn at two (2) timepoints in the study – one blood draw (amounting to 4 tubes, 7 ml each) will be done prior to the start of treatment with Pylera® plus PPI (presumed to be omeprazole) (Inclusion Visit), and a second blood draw sample (amounting to 4 tubes, 7 ml each) the day after the end of treatment with Pylera® plus PPI (EOT Visit). The date and time of the two blood samplings will be recorded and reported for each subject. The collection tubes will be shielded from light to minimize photo-degradation and frozen at -20°C before transport for measurement of bismuth and TMB concentration.

2) Type of tubes
Blood samples will be obtained from an antecubital vein using two types of tubes:

- For bismuth plasma concentration determination: coded EDTA K2 Vacutainers tubes or equivalent (1 x 7 mL tube),
- For bismuth whole blood concentration determination: coded sodium citrate-coated Vacutainer tubes or equivalent (1 x 7 mL tube).
- For TMB whole-blood concentration determination: coded sodium citrate-coated Vacutainer tubes or equivalent (2 x 7 mL tubes).

3) Processing
Processing of one (1) blood sample per patient for bismuth plasma concentration determination:
Following collection, each 7 mL EDTA tube will be centrifuged at 4ºC and 1500 g for 10 minutes; the resulting plasma will be extracted and divided into even numbers of opaque polypropylene snap-cap tubes (minimum two tubes) and frozen at a minimum of -20°C until shipment to the central laboratory for analysis of bismuth plasma concentrations.
Processing of one (1) blood sample per patient for bismuth whole blood concentration determination:

The 1 x 7 mL sample will be drawn on citrate-coated tubes not centrifuged, protected from light and frozen at -20°C before transport for whole blood measurement of bismuth.
Processing of two (2) blood samples per patient for TMB whole-blood concentration determination:
The 2 x 7 mL samples will be drawn on citrate-coated tubes not centrifuged, protected from light and frozen at -20°C before transport for whole-blood measurement of TMB.

4) Transport and concentration determination
All sample tubes will be labeled with the study identification number, subject identifier, and time of sampling. Samples will be stored in an opaque box and frozen at a minimum of -20°C until shipment to the central laboratory. Transfer to the central laboratory will be done by an approved transporter under frozen conditions and with samples being shielded from exposure to light.

The central laboratory will receive and store all shipped samples and will distribute plasma and whole blood samples to the analytical facilities for analysis of total bismuth. The TMB metabolite concentration determination will be determined once bismuth concentration is known.

5) Additional third blood sample
This sampling and processing procedure will also be used only if a subject is requested to return to provide a third confirmatory plasma and whole blood sample for bismuth analysis in case of clinical symptoms indicative of bismuth-related neurological adverse events or bismuth accumulation at the EOT Visit (total bismuth in whole blood > 50 µg/L).

APPENDIX 3 – CENTRAL NERVOUS SYSTEM ADVERSE EVENTS OF INTEREST

Bismuth neurotoxicity is typically characterized by encephalopathy, which is defined as any degenerative or diffuse disease of the brain that alters brain structure or function.

In order to select the appropriate terms, the original Standardized MedDRA Query (MedDRA 15.1SMQ Noninfectious encephalopathy/delirium (20000133)) was revised to specifically address the bismuth encephalopathy and include signs and symptoms that are specific to this risk.

Preferred Terms (narrow scope): Encephalopathy, Toxic encephalopathy

Preferred Terms (broad scope):

Abnormal behavior; Agitation; Agraphia; Alexia; Altered state of consciousness; Amnesia; Anal sphincter atony; Apathy; Ataxia; Bladder sphincter atony; Cerebellar ataxia; Cerebellar syndrome; Clonic convulsion; Coma; Coma scale abnormal; Complex partial seizures; Confusional state; Convulsion; Convulsions local; Coordination abnormal; Delirium; Depressed level of consciousness; Disturbance in attention; Dysarthria; Dysgraphia; Dyspraxia; Faecal incontinence; Gait apraxia; Gait disturbance; Generalised non-convulsive epilepsy; Grand mal convulsion; Hallucination; Hallucination, auditory; Hallucination, gustatory; Hallucination, olfactory; Hallucination, synaesthetic; Hallucination, tactile; Hallucination, visual; Hallucinations, mixed; Hypersomnia; Hyporesponsive to stimuli; Illogical thinking Incontinence ; Judgement impaired; Lethargy; Listless; Loss of consciousness; Memory impairment; Mental impairment; Mental status changes; Mood altered; Myoclonus; Paresis anal sphincter; Partial seizures; Partial seizures with secondary generalization; Personality change; Personality disorder; Psychomotor seizures; Restlessness; Simple partial seizures; Sleep disorder; Slow response to stimuli; Sluggishness; Somnolence; Speech disorder; Stupor; Thinking abnormal; Tonic convulsion; Tremor; Unresponsive to stimuli; Urinary incontinence.

A “narrow” scope represents the condition of interest and a “broad” scope helps to identify all possible cases, including some that may prove to be of little or no interest on closer inspection. Thus, a “narrow” search yields “specificity” while the “broad” search yields “sensitivity.”

The presence of these events will be identified and assessed at the End of Treatment and End of Study visits only as the event would need to be treatment-emergent in order to be potentially associated with potential bismuth neurotoxicity.

Of note is the follow-up for serious adverse events (SAEs) of encephalopathy, which will be ensured through a separate intensive monitoring program comprising a “neurological disorders and bismuth” questionnaire (specific to the Intensive Monitoring Program and not part of this study) to be completed for each case, followed by case review and confirmation by the Scientific Committee of the Intensive MonitoringProgram.

17 AMENDEMENTS

AMENDMENT N°1

AMENDMENT N°2

AMENDMENT N°3

AMENDMENT N°4

AMENDMENT NO. 1

The table below describes the changes introduced in this amendment. The left column identifies the section where the change was made and the right column describes the change introduced. Apart from the changes described in the table below, this amendment includes the following:

- Corrected a few typographic errors in the protocol.

Sections	Text that was deleted (~~**deleted**~~) or added (***added***) from the original protocol dated 12 JUL 2012
PROTOCOL/AMENDMENT APPROVAL PAGE	***Pr Moore, coordinating principal investigator*** ~~**George Harb, Senior Director**~~ ***Dr Ruth Thieroff-Ekerdt, Chief Medical Officer***
IMPORTANT CONTACTS	The list and contact information involved in the study has been updated. ***PD Dr Johannes Lampe, Medical Monitor*** ***Sonia Neau, Study Manager***

AMENDMENT NO. 2

The table below describes the changes introduced in this amendment. The left column identifies the section where the change was made and the right column describes the change introduced. Apart from the changes described in the table below, this amendment includes the following:

- Corrected a few typographic errors in the protocol.

Sections	Text that was deleted (~~**deleted**~~) or added (***added***) from the previous amended protocol dated 05 OCT 2012
THROUGHOUT THE DOCUMENT	Throughout the document wording has been changed: ~~**Urease breath test (UBT)**~~ ***a diagnostic H. pylori test (breath test, biopsy, or other test at the discretion of the Investigator)*** Vital sign measurements, we delete: ~~**Respiratory rate, and body temperature**~~ We remove: ~~**Physical examination**~~ ~~**Electronic CRF**~~ ***CRF*** ~~**Initial visit**~~ ***Inclusion visit***
IMPORTANT CONTACTS	The list and contact information involved in the study has been updated. ~~**Maï Luong, Manager Pharmacovigilance**~~ ***Alexandru Iacob, Drug Safety Physician*** ~~**Pr Moore, coordinating principal investigator**~~ ***Nicholas Moore MD, PhD, Scientific Leader*** Contact at Lampe and ~~**Konieczny**~~ ***Company,*** PD Dr Johannes Lampe**,** ~~**j.lampe@lampekonieczny.com,**~~ ***j.lampe@lampeandcompany.com***

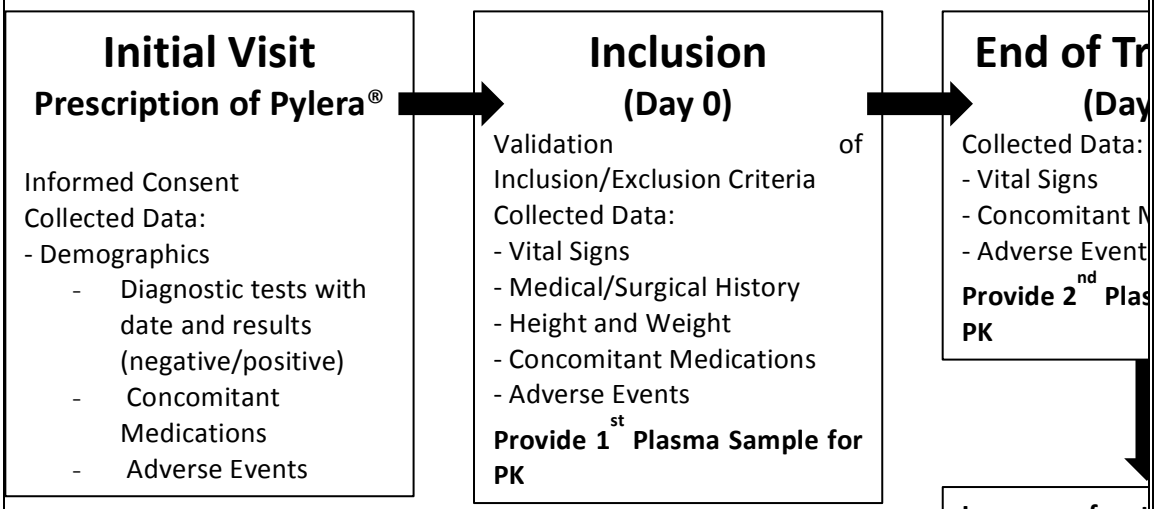
STUDY SYNOPSIS	Study Procedures: Subjects will provide two blood samples for assessment of bismuth plasma concentrations ***(total bismuth and trimethylbismuth)***, with one sample provided prior to start of Pylera® treatment and one sample provided ~~**the**~~ day 11 ***i.e. Day 1*** after completion of Pylera® treatment. If accumulation of bismuth is detected ***(defined as plasma bismuth concentration exceeding 50µg/L)***, subjects will be contacted to ***immediately*** return ~~**immediately**~~ to the laboratory to draw a third verification sample and will be referred for potential inclusion and follow-up in a separate Intensive Monitoring Program. ***In case of neurological AE indicative of bismuth encephalopathy (please refer to Appendix 3 – Central Nervous System Adverse Events of Interest) if present at Day 11 blood samples will be as quickly processed as possible. A diagnostic H. pylori test to assess H. pylori eradication should be repeated on one single occasion at least 28 days post-treatment.*** ~~**A subject will be evaluated and followed up for possible bismuth accumulation if the subject's plasma bismuth concentration exceeds 50 µg/L.**~~ ~~**Study endpoints**~~ **:** ~~**Primary Efficacy Endpoint:**~~ ~~**Not applicable; this study is intended to assess the population PK of bismuth following treatment with Pylera® in real-life practice.**~~ ~~**Secondary Efficacy Endpoints:**~~ ~~**Eradication efficacy of Pylera® as measured by UBT conducted at least 28 days following the end of treatment with Pylera®, in patients with initially positive H. pylori tests.**~~ ~~**Safety profiles as measured by vital signs, physical examinations, reported adverse events (AEs), and reported encephalopathies in treatment successes and treatment failures.**~~ Efficacy and safety variables: ~~**Of note is the follow-up for serious adverse events (SAEs) of encephalopathy, which will be ensured through a separate intensive monitoring program comprising a "neurological disorders and bismuth" questionnaire to be completed for each case, followed by case review and confirmation by the Scientific Committee of the Intensive Monitoring Program. Evaluation between bismuth concentration and occurrence of neurological symptoms will be provided as such in the Periodic Safety Update Reports, PSUR) or within the reports of the intensive monitoring program.**~~

SECTION 2	~~**2.2 PRIMARY EFFICACY ENDPOINT**~~ ~~**Not applicable; this study is intended to assess the population PK of bismuth following treatment with Pylera® in real-life practice.**~~ 2.2 SECONDARY OBJECTIVES 1. To evaluate treatment effectiveness by the eradication measured by a negative ~~**second**~~ diagnostic *H. pylori* test (breath test, biopsy, or other test at the discretion of the Investigator) for subjects with an initially positive ~~**infection**~~ ***H. pylori*** test. 2. To compare post-treatment bismuth concentrations in treatment successes and failures. 3. To evaluate the accumulation of bismuth in subjects receiving Pylera® with omeprazole *versus* subjects who may have received Pylera® with another proton pump inhibitor (PPI) other than omeprazole. 4. To compare population safety data profiles in treatment successes and failures. ~~**2.4** ***2.3*** **SECONDARY** ***SAFETY AND EFFICACY VARIABLE*** **ENDPOINT**~~ ~~**Eradication efficacy of Pylera® as measured by UBT conducted at least 28 days following the end of treatment with Pylera®, in patients with initially positive** ***H. pylori*** **tests.**~~ **2.3.*1 Safety Variables*** ***The safety profile will be assessed in terms of overall AEs, vital signs, and concomitant medication usage over the 10-day treatment period, as well as at the 4 weeks follow-up period after treatment.*** ***There will be an additional follow-up for neurological adverse events (AEs) indicative of encephalopathy.***

SECTION 2	~~*2.5 SECONDARY SAFETY ENDPOINT*~~ ~~Safety profiles as measured by vital signs, physical examinations, reported AEs, and reported encephalopathies in treatment successes and tretament failures.~~ ***2.3.2 Efficacy Variables*** ***A post-treatment diagnostic H. pylori test for eradication (e.g. breath test, biopsy or other test at the discretion of the Investigator).***
SECTION 3	3.1 OVERALL STUDY DESCRIPTION The subject study period will be conducted at these participating sites and will be comprised of ~~**four**~~ ***three*** steps as follows: ~~**1. Initial Visit following decision by investigator to prescribe Pylera®**~~ ~~**2. Inclusion (Day 0)**~~ ~~**3. End of Treatment Period (EOT) Visit (Day 11)**~~ ~~**4. End of Study (EOS) Visit (Day 39)**~~ ***1.Inclusion Visit (Day 0)*** ***2.End of Treatment Period (EOT) Visit (Day 11)*** ***3.End of Study (EOS) Visit (Day 39)*** ***An allowance for participation will be provided to each patient at the end of the 3rd visit.***

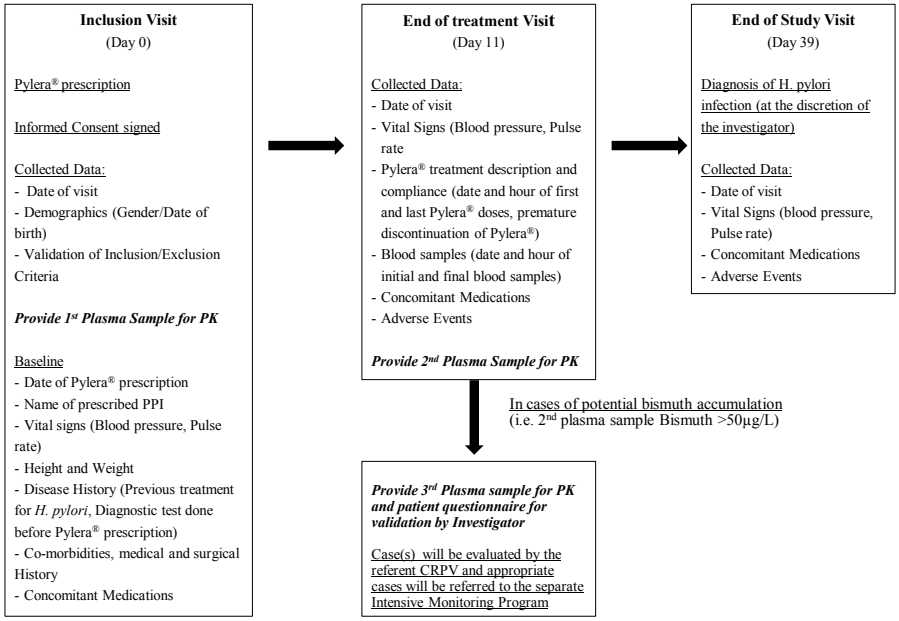
SECTION 3

~~**OLD VERSION:**~~



SECTION 3

NEW VERSION:



3.2 SCHEDULING OF VISIT

~~**Information regarding demographic data, physical examinations, height, weight, vital signs, and medical and surgical history – including information pertaining to prior *H. pylori* treatment – will be surveyed, as well as information concerning diagnostic procedures performed to verify *H. pylori* infection. Screening period should not exceed 15 days**~~.

Information regarding date of Pylera® prescription, name of prescribed PPI, demographic data, vital signs, height, weight, disease history for H. pylori infection (including information pertaining to prior H. pylori treatment), co-morbidities, medical and surgical history — will be surveyed, as well as information concerning diagnostic procedures performed to verify H. pylori infection.

SECTIONS 3, 4	Subjects who demonstrate clinical symptoms indicative of bismuth-related neurological adverse events or bismuth accumulation at the EOT Visit (total bismuth in plasma > 50 µg/L) will be requested to return to the laboratory immediately to draw a third blood sample for evaluation of bismuth. ***Subjects having clinical symptoms indicative of bismuth-related neurological adverse events will be referred to the separate Intensive Monitoring Program.*** If bismuth concentration remains sustained ***in subjects with no neurological symptoms*** and subject interview with Investigator confirms that no third-party source of bismuth was consumed outside of the context of this study, the subject will be referred to the separate Intensive Monitoring Program to be evaluated for inclusion. 4.3 CONCOMITANT MEDICATION 4.3.1 Previous and Concomitant Medication The brand name (or if unknown, the generic name), ~~**dose**~~, dose unit (or dosage form if a compound medication), frequency, ~~**route of administration, duration of use (**~~start date and, if applicable, stop date ~~**and indication**~~ for all previous medications (taken 3 months prior to Informed Consent Form [ICF] signature) and concomitant medications (taken at the time of the ICF signature and during the course of the study) must be documented in the Case Report Form (CRF). Medications include prescription medications, intravenous fluids, herbals, vitamins, and any other over-the-counter medicines.

SECTION 7, 8	7 ADMINISTRATIVE PROCEDURES AND ETHICAL CONSIDERATIONS ~~**The investigator must agree to maintain a record of all drug received and dispensed, using the Drug Accountability from provided by APTALIS PHARMA US, INC.**~~ ***The Investigator must document in the CRF, Pylera® treatment description and compliance: date of first dose, date and hour of last dose, premature discontinuation of Pylera®, and if the subject took all doses.*** 7.8 PROTOCOL AMENDMENTS AND OTHER CHANGES IN STUDY CONDUCT ~~**Minor changes in the packaging or labeling of study drug**~~ 8 MATERIAL ***AND STUDY DRUG*** Not applicable. This study is designed to capture pharmacokinetics information on bismuth in a naturalistic real-world setting. No study medication *per se* will be distributed during the course of this study. ***The patient will be instructed to take the Pylera® as prescribed by the Investigator.***

SECTION 9	9.1 ~~**PRETREATMENT**~~ ***INCLUSION*** PROCEDURES 9.1.2 Observations and measurements ~~**9.1.2.1 Screening procedures**~~ Following the granting of Informed Consent, each subject will be assigned a subject number in sequential order. The following Inclusion Visit procedures and evaluations in addition to procedures normally conducted as part of standard of care will be performed after Informed Consent~~, **and results**~~ will be recorded in the appropriate sections of the CRF: ~~• **Demographic data**~~ ~~• **Diagnostic tests with date and results (negative/positive)**~~ ~~• **Recording of prior and concomitant medications**~~ ~~• **Recording of AEs**~~ • ***Demographic data*** • ***Confirmation of inclusion and exclusion criteria*** • ***Date of Pylera® prescription*** • ***Name of prescribed PPI*** • ***Vital signs measurement (blood pressure, pulse rate,) height and weight*** • ***Disease history regarding H. pylori infection with previous H. pylori treatment and diagnostic tests with date and results (negative/positive)*** • ***Co-morbidities, medical/surgical history*** • ***Recording of prior and concomitant medications*** ***Subjects will provide one blood sample as the baseline sample (D0 sample) for assessment of plasma bismuth concentrations and whole blood trimethylbismuth (TMB) concentrations as per the procedures outlined in Appendix 2.***

SECTION 9	***Once the D0 sampling is complete, subjects will be given an appointment for the second blood sampling (D11 sample) and subjects may initiate treatment with Pylera®.*** ~~**9.1.2.2**~~ ***9.1.3*** Randomization Procedures ~~**Not applicable as this is an open-label, single-arm study.**~~ ***There is no randomization procedure as this is an open-label, single-arm study.*** 9.2 DURING TREATMENT PROCEDURES • ***Recording of AEs in case a patient contact the Investigator*** ~~**Upon confirmation of subject eligibility, the following will be completed as part of the Treatment Visit:**~~ ~~**• Confirmation of inclusion and exclusion criteria**~~ ~~**• Vital sign measurement (pulse rate, blood pressure, respiratory rate, and body temperature)**~~ ~~**• Physical examination**~~ ~~**• Medical/surgical history (including information pertaining to prior *H. pylori* treatment.)**~~ ~~**• Height and weight**~~ ~~**• Recording of concomitant medications**~~ ~~**• Recording of AEs**~~ ~~**Subjects will provide one blood sample as the baseline sample (T0 sample) for assessment of plasma bismuth concentrations as per the procedures outlined in Appendix 2.**~~ ~~**Once the T0 sampling is complete, subjects will be given an appointment for the second blood sampling (D11 sample) and subjects may initiate treatment with Pylera®.**~~

SECTION 9	***9.2.1 Subjects who completed treatment with Pylera®*** ***Subjects who have completed the 10-day treatment with Pylera® will return to complete the following procedures as part of the EOT Visit:*** • ***Vital signs measurement (blood pressure, pulse rate)*** • ***Recording Pylera® treatment description and compliance*** • ***Recording of concomitant medications*** • ***Recording of AEs*** ***The presence of CNS adverse events of specific interest as listed in Appendix 3 will be assessed at this visit with the specific form "Pharmacovigilance reporting form-neurological disorders and bismuth" developed for the collection of the adverse events of special interest as part of the Intensive Monitoring Program that will be completed by the Investigator.*** ***Subjects will provide one blood sample as the post-treatment sample (D11 sample) for assessment of plasma bismuth concentrations and whole blood TMB concentrations as per the procedures outlined in Appendix 2.*** ***Subjects who demonstrate bismuth accumulation at the EOT Visit (> 50 µg/L) will be requested to return immediately to the laboratory to draw a third blood sample for evaluation of bismuth. If bismuth concentration remains sustained and subject interview with Investigator confirms that no third-party source of bismuth was consumed outside of the context of this study, the subject will be referred to the separate Intensive Monitoring Program to be evaluated for inclusion.*** ***Subjects will return 28 days after the EOT Visit to complete the EOS Visit. At this visit, subjects will complete:*** • ***Vital signs measurement (blood pressure, pulse rate)*** • ***Recording eradication test*** • ***Recording of concomitant medications*** • ***Recording of AEs***

SECTION 9

The presence of CNS adverse events of specific interest as listed in Appendix 3 will be assessed at this visit with a specific questionnaire "Pharmacovigilance reporting form-neurological disorders and bismuth" that will be completed and validated by the Investigator.

Subjects who demonstrate a positive diagnostic H. pylori test (breath test, biopsy, or other test at the discretion of the Investigator) at End of Study will be documented by the completion of a specific form entitled "Targeted follow-up form – Pylera® eradication therapy failure". These subjects will be referred to treatment for H. pylori infection outside of the context of this study.

9.2.2 Subjects who prematurely discontinue treatment with Pylera®

For any subject who prematurely discontinues treatment with Pylera®, the Investigator will perform the EOS procedures and will complete appropriate pages of the CRF. A diagnostic H. pylori test (breath test, biopsy, or other test) will be conducted at the discretion of the Investigator.

In case of withdrawal of consent, only the date of and the reason for withdrawing consent will be collected on the CRF. Otherwise, the Investigator will make all reasonable effort to complete as much as possible the following at the time of discontinuation.

#	*Information to be collected*
1	*Vital sign measurements (pulse rate, blood pressure measured from the same arm throughout the study)*
2	*Record of any occurrence of AEs, change in concurrent medical conditions, use of adjunctive therapy/procedure, and intake of concomitant medication*
3	*Collect safety information via a phone call to the patient 30 ± 5 days after discontinuation (includes AEs, change in concurrent medical conditions, use of adjunctive therapy/procedures, and intake of concomitant medication).*
4	*A diagnostic H. pylori test (breath test, biopsy, or other test) at the discretion of the Investigator*

SECTION 9	***All results of evaluation and observations, together with the reason for withdrawal from the study, will be recorded on the CRF.*** ***For any subject who prematurely discontinues treatment with Pylera® due to a neurological AE indicative of bismuth encephalopathy, the subject will be followed up through a separate Pylera® Intensive Monitoring Program.*** **~~9.3 END-OF-TREATMENT/END OF STUDY PROCEDURES~~** ***CLINICAL LABORATORY PROCEDURES*** ***Not applicable*** **~~9.3.1Subjects who completed treatment with Pylera®~~** **~~Subjects who have completed the 10-day treatment with Pylera® will return to complete the following procedures as part of the EOT Visit:~~** **~~• Vital sign measurement (pulse rate, blood pressure, respiratory rate, and body temperature)~~** **~~• Physical examination~~** **~~• Recording of concomitant medications~~** **~~• Recording of AEs~~** **~~• Recording of date and time of last dose of Pylera® taken by subject~~** **~~The presence of CNS adverse events of specific interest as listed in Appendix 3 will be assessed at this visit with a specific questionnaire that will be completed by the subject and validated by the investigator.~~** **~~Subjects will provide one blood sample as the post-treatment sample (D11 sample) for assessment of plasma bismuth concentrations as per the procedures outlined in Appendix 2.~~**

SECTION 9	~~Subjects who demonstrate bismuth accumulation at the EOT Visit (> 50 µg/L) will be requested to return to the laboratory to draw a third blood sample for evaluation of bismuth. Subjects will be re-assessed for AEs and CNS AEs of special interest (if any) as listed in Appendix 3 with a specific questionnaire which will be completed by the subject and validated by the Investigator. If bismuth concentration remains sustained and subject interview with investigator confirms that no third-party source of bismuth was consumed outside of the context of this study, the subject will be referred to the separate intensive monitoring program to be evaluated for inclusion.~~ ~~Subjects will return 28 days after the EOT Visit to complete the EOS Visit. At this visit, subjects will complete:~~ ~~• UBT (test date and results)~~ ~~• Vital sign measurement (pulse rate, blood pressure, respiratory rate, and body temperature)~~ ~~• Physical examination~~ ~~• Recording of concomitant medications~~ ~~• Recording of AEs~~ ~~The presence of CNS adverse events of specific interest as listed in Appendix 3 will be assessed at this visit with a specific questionnaire that will be completed by the subject and validated by the investigator.~~ ~~Subjects who demonstrate a positive UBT at End of Study will be documented by the completion of a specific form entitled "Targeted follow-up form – Pylera eradication therapy failure". These subjects will be referred to treatment for *H. pylori* infection outside of the context of this study.~~ ~~9.3.2Subjects who prematurely discontinue treatment with Pylera®~~ ~~For any subject who prematurely discontinues treatment with Pylera®, the investigator will perform the EOS procedures will complete appropriate pages of the CRF. UBT will be conducted at the discretion of the investigator.~~

SECTION 9

~~**In case of withdrawal of consent, only the date of and the reason for withdrawing consent will be collected. Otherwise, the investigator will make all reasonable effort to complete as much as possible the following at the time of discontinuation.**~~

#	~~**Information to be collected**~~
1	~~**Vital sign measurements (pulse rate, blood pressure measured from the same arm throughout the study, respiratory rate, and body temperature after a 5-minutes rest in a sitting position)**~~
2	~~**Physical examination**~~
2	~~**Record of any occurrence of AEs, change in concurrent medical conditions, use of adjunctive therapy/procedure, and intake of concomitant medication**~~
3	~~**Collect safety information via a phone call to the patient 30 ± 5 days after discontinuation (includes AEs, change in concurrent medical conditions, use of adjunctive therapy/procedures, and intake of concomitant medication).**~~
4	~~**UBT, at the discretion of the investigator**~~

~~**All results of evaluation and observations, together with the reason for withdrawal from the study, will be recorded on the CRF.**~~

~~**For any subject who prematurely discontinues treatment with Pylera® due to a neurological AE suggestive of bismuth encephalopathy, the subject will be followed up through a separate Pylera® intensive monitoring program.**~~

SECTION 9	~~**9.4CLINICAL LABORATORY PROCEDURES**~~ ***OTHER PROCEDURES*** ~~**Not applicable.**~~ ***A diagnostic H. pylori test (breath test, biopsy, or other at the discretion of the Investigator)*** ***Presence of H. pylori will be assessed at the EOS Visit. The selection of the method for this assessment is at the discretion of the Investigator.*** ~~**9.5OTHER PROCEDURES**~~ ~~**Urea Breath Test (UBT)**~~ ~~**Presence of *H. pylori* will be assessed at the EOS Visit by a commercially-available UBT conducted as per kit instructions.**~~

SECTION 10

10.1 DEFINITIONS

An **Unexpected Adverse Event** is defined as an adverse drug event, the nature or incidence of which is not consistent with applicable reference safety information (Pylera® SmPC [~~**2 September 2011**~~ ***18 May 2012***]; omeprazole Summary of Product Characteristics [February 2008]).

10.4.1 ASSESSMENT AND RECORDING

At each follow-up visit or assessment by phone or otherwise, all AEs, whether observed by the Investigator or one of his or her professional collaborators, or reported by the subject spontaneously or in response to an open question, will be recorded in the Adverse Event Form included in the CRF with the following information.

- **Name of the AE**: Name should be a medical term. When possible, the investigator should differentiate an illness entity from isolated symptoms or signs. For instance, the term "flu" should be recorded instead of listing all the flu-related symptoms. Where a differentiation is not possible, symptoms and signs should be separately recorded and evaluated as adverse events.

- ~~**Date of onset of the AE**~~ ***Start date and stop date (or statement that the event is continuing) of the AE***

- ~~**Intensity: Event intensity must be assessed according to the following three categories.**~~

~~**Intensity**~~	~~**Definition**~~
~~**Mild**~~	~~**Noticeable to the subject, does not interfere with the subject's daily activities, usually does not require additional therapy, dose reduction, or discontinuation of the study.**~~
~~**Moderate**~~	~~**Interferes with the subject's daily activities, possibly requires additional therapy, but does not require discontinuation of study.**~~
~~**Severe**~~	~~**Severely limits the subject's daily activities and may require discontinuation of the study.**~~

SECTION 10, 11	~~• Date of resolution (or statement that the event is continuing);~~ • *Imputability of Pylera®: evaluate the causal relationship between Pylera® and the AE as described in section 10.4.2* • *Seriousness criteria as defined in section 10.1* ~~Action taken (e.g. concomitant medication or adjunctive therapy/procedure given will be recorded on the concomitant medication form or adjunctive therapy/procedure form of the CRF, respectively)~~ ~~• Subject outcome~~ ~~• Whether the event meets the definition of a SAE (see Section 10.1)~~ 10.4.3.3 Other reportable events ~~An AE of encephalopathy will be reported via a specific "neurological disorders and bismuth" questionnaire, which will followed by case review and confirmation by the Scientific Committee of a separate intensive monitoring program. Evaluation between bismuth concentration and occurrence of neurological symptoms will be provided as such in the Periodic Safety Update Reports (PSURs) or within the reports of the intensive monitoring program~~ ***There will be an additional follow-up for neurological adverse events indicative of encephalopathy through a separate and concomitant safety program, i.e. the Intensive Monitoring Program, as part of Risk management plan of Pylera®. A "Pharmacovigilance reporting form – for neurological events with bismuth" shall be completed for each case where neurological symptoms listed in the Appendix 3, accompanied or not by bismuth plasma concentrations above 50 µg/L occur. There will be a case review and confirmation by the Scientific Committee of the Intensive Monitoring Program for the diagnosis of encephalopathy. The assessment of the correlation between bismuth concentration and occurrence of neurological symptoms will be provided in the Periodic Safety Update Reports (PSUR) and in the reports from the Intensive Monitoring Program.*** 11.2 INTERIM ANALYSIS The analysis will be conducted to present the summary of the derived population PK parameters and the Confidence Interval. If low variability is found, the sponsor and the study project team will ~~envision~~ stop~~ping~~ the study at 100 subjects***, after consultation with Regulatory Agency***.

SECTION 11	11.4.1 Data capture The progress of the study will be monitored by ~~**on-site and**~~ telephone communication between site personnel and an Aptalis Pharma US, Inc. designee. On-site visits will be performed at ***the end of the study*** ~~**intervals deemed necessary**~~ to ensure compliance with the study protocol and to perform review of the subject CRF against the source document (subjects' medical record). On-site visits will also ensure that adequate records of clinical study supplies are maintained and to assess the continued suitability of the site. 11.7.3 Analysis of Baseline and Demographic Data Inclusion data with subject demographic information will be summarized using descriptive statistics for quantitative variables (e.g., weight, height, age) and counts and percentages for categorical variables (e.g., sex~~**, race**~~). 11.7.6 Safety analysis ~~**Of note is the follow-up for serious adverse events (SAEs) of encephalopathy, which will be ensured through a separate intensive monitoring program comprising a "neurological disorders and bismuth" questionnaire to be completed for each case, followed by case review and confirmation by the Scientific Committee of intensive monitoring program. Evaluation between bismuth concentration and occurrence of neurological symptoms will be provided as such in the Periodic Safety Update Reports (PSURs) or within the reports of the intensive monitoring program**~~ ***There will be an additional follow-up for neurological adverse events indicative of encephalopathy through a separate and concomitant safety program, i.e. the Intensive Monitoring Program, as part of Risk management plan of Pylera®. A "Pharmacovigilance reporting form – for neurological events with bismuth" shall be completed for each case where neurological symptoms listed in the Appendix 3, accompanied or not by bismuth plasma concentrations above 50 µg/L occur. There will be a case review and confirmation by the Scientific Committee of the Intensive Monitoring Program for the diagnosis of encephalopathy. The assessment of the correlation between bismuth concentration and occurrence of neurological symptoms will be provided in the Periodic Safety Update Reports (PSUR) and in the reports from the Intensive Monitoring Program.***

SECTION 13	In our internal SOP this section has changed: 13 PUBLICATION POLICY ~~**All information concerning the study and related to APTALIS PHARMA US, Inc. operations, such as patent applications, manufacturing processes, basic scientific data, assay methods, and formulation information supplied by APTALIS PHARMA US, Inc. and not previously published, is considered confidential by APTALIS PHARMA US, Inc. and shall remain the sole property of the sponsor. The investigator agrees to use this information only for the purpose of undertaking this study, and will not use it for any other purpose without prior written consent from APTALIS PHARMA US, Inc.**~~ ~~**The data from this clinical study will be used by APTALIS PHARMA US, Inc. in connection with the development of the research program and may be disclosed as required to other clinical investigators, to the HPFB, FDA, EMA, and to government regulatory agencies in other countries. Hence, it is understood by the investigator that there is an obligation to provide APTALIS PHARMA US, Inc. with complete test results and all data developed in this study.**~~ ~~**A final clinical/statistical report namely for the purpose of filings with appropriate governmental agencies (such as the FDA, the European Union member states and others) will be prepared once the data from all Study sites has been received (the "Report"). The Report will contain a description of the efficacy/safety and other relevant data and its analysis ("Results").**~~ ~~**APTALIS PHARMA US, Inc. is committed to ensure that publications of all of its clinical trial results in biomedical journals are done in a timely manner, regardless of the Results. Publications should follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE)[36] and the Pharmaceutical Research and Manufacturers of America (PhRMA)[37] and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals (http://www.icmje.org). APTALIS PHARMA US, Inc. is committed to ensuring that authorship for all publications comply with the criteria defined by the ICMJE**~~.

SECTION 13	~~**Since this is a multicentre study, a study publication group composed of different investigators with a key involvement in the Study and representatives of APTALIS PHARMA US, Inc.'s Global Medical Affairs Department (the "Study Publication Group"), will be created and it will be the Study Publication Group's responsibility to identify the individuals who accept direct responsibility for the primary abstract and/or manuscript (the "Primary Manuscript"). These individuals should fully meet the criteria for authorship referred to above. Other members of the Study Publication Group should be listed in the acknowledgments if and as appropriate. The development, review and submission of the Primary Manuscript will be done in accordance with APTALIS PHARMA US, Inc.'s Standard Operating Procedure entitled "Preparation and Submission of Scientific, Technical and Medical Publications". Presentation or publication of data subsets from individual institutions participating in the multicenter trials ("Individual Manuscripts") should not precede the Primary Manuscript, without APTALIS PHARMA US, Inc.'s prior written consent, unless the Primary Manuscript is not published within twenty four (24) months after the Site close-out visit. All proposed Individual Manuscripts will be submitted to APTALIS PHARMA US, Inc. at least sixty (60) days prior to submission, for prior review by APTALIS PHARMA US, Inc.**~~ ~~**(i) to allow APTALIS PHARMA US, Inc. to identify any Confidential Information, excluding Results, which must be removed from the Individual Manuscript prior to publication or presentation;**~~ ~~**(ii) to ensure accuracy of the data and analyses being published or presented, and**~~ ~~**(iii) to allow APTALIS PHARMA US, Inc. to identify any information requiring intellectual property protection prior to publication or presentation.**~~ ~~**In the event APTALIS PHARMA US, Inc. identifies any information requiring intellectual property protection, Institution and/or Principal Investigator (PI) agrees to delay publication or presentation of the Individual Manuscript for an additional period not to exceed ninety (90) days in order for APTALIS PHARMA US, Inc. to secure appropriate intellectual property protection. Except as otherwise provided under this Section, the PI will be under no obligation to modify the Individual Manuscript and will retain full control over its publication, including where it is published.**~~

SECTION 13	~~**APTALIS PHARMA US, Inc. is authorized to freely use and distribute the Primary Manuscript and Individual Manuscripts as needed, after their publication, without any other obligation. Insofar as required, APTALIS PHARMA US, Inc. is therefore granted a free license for an unlimited duration and territory.**~~ ***Aptalis Pharma designs and conducts clinical studies in an ethical and scientifically rigorous manner to determine the benefits, risks, and value of pharmaceutical products. Aptalis Pharma US, Inc is responsible for receipt and verification of data from all research sites for Aptalis Pharma US, Inc's studies, to ensure the accuracy and integrity of the entire study database, which is owned by Aptalis Pharma US, Inc.*** ***Aptalis Pharma US, Inc is committed to ensure that publication of all of its clinical studies results in biomedical journals are done in a timely manner, regardless of the study results. Publications should follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals (http://www.icmje.org). is committed to ensuring that authorship for all publications comply with the criteria defined by the ICMJE.*** ***Clinical studies may involve already marketed products and/or investigational products. Aptalis Pharma US, Inc is committed to the timely submission and registration on a public database (e.g.Clintrials.gov) of summary information concerning relevant clinical studies that Aptalis Pharma US, Inc is conducting. These clinical studies will involve use of Aptalis Pharma US, Inc's marketed or investigational products. Aptalis Pharma US, Inc is also committed to the timely submission and posting of summary results of all clinical studies conducted in subjects involving the use of Aptalis Pharma US, Inc's products that are approved for marketing, or that are investigational products whose development programs are discontinued, regardless of outcome.*** ***The publication rights of the investigators for this study are set forth in the individual agreements with each clinical sites.***

APPENDIX 1

~~APPENDIX 1 – STUDY FLOWCHART~~

	~~Screening Visit~~	~~Treatment Visit (Day 0)~~	~~End of Treatment (Day 11 + 3 days)~~	~~End of Study (Day 39 + 28 days)~~
~~Informed Consent~~	~~X~~			
~~Demographics~~	~~X~~			
~~Diagnostic tests with date and results (negative/positive)~~[1]	~~X~~			
~~Medical/surgical history~~[1]		~~X~~		
~~Height, weight~~		~~X~~		
~~Physical examination~~		~~X~~	~~X~~	~~X~~
~~Vital Signs~~		~~X~~	~~X~~	~~X~~
~~Inclusion/Exclusion criteria~~		~~X~~		
~~UBT~~				~~X~~[2]
~~Prior and concomitant medications~~	~~X~~	~~X~~	~~X~~	~~X~~
~~Pharmacokinetics sample~~		~~X~~	~~X~~[3]	
~~Adverse events~~	~~X~~	~~X~~	~~X~~	~~X~~
~~CNS adverse events~~			~~X~~	~~X~~

~~1. Including information pertaining to prior *H. pylori* treatment.~~

~~2. A unique UBT will be performed at End of Study at least 28 days post treatment.~~

~~3. Subjects who demonstrate bismuth accumulation at the End of Treatment Visit (> 50 µg/L) will be requested to return to the laboratory to draw a third blood sample for evaluation of bismuth. If bismuth concentration remains sustained and subject interview with investigator confirms that no third-party source of bismuth was consumed outside of the context of this study, the subject will be referred to the separate intensive monitoring program to be evaluated for inclusion.~~

APPENDIX 1

APPENDIX 1 - STUDY FLOWCHART

	Inclusion Visit (Day 0)	*End of Visit (Day 11)*	*End of Study Visit (Day 39)*
Informed Consent	***X***		
Demographics	***X***		
Inclusion/Exclusion criteria	***X***		
Vital Signs	***X***	***X***	***X***
Diagnostic tests done before Pylera® prescription[1]	***X***		
Co-morbidities, medical, surgical history	***X***		
Concomitant medications	***X***	***X***	***X***
Diagnostic H. pylori test (breath test, biopsy, etc)	***X***		***X[2]***
Pharmacokinetics sample	***X***	***X[3]***	
Adverse events		***X***	***X***
CNS adverse events[4]		***X***	***X***

1. ***Including information pertaining to prior H. pylori treatment.***
2. ***At the discretion of the Investigator***
3. ***Subjects who demonstrate bismuth accumulation at the End of Treatment Visit (> 50 µg/L) will be referred to the separate Intensive Monitoring Program to be evaluated for inclusion. In case of inclusion, patients will be requested to return to the laboratory to draw a third blood sample for evaluation of bismuth). In case of neurological AE indicative of bismuth encephalopathy (please refer to Appendix 3 – Central Nervous System Adverse Events of Interest) if present at Day 11 blood samples will be as quickly processed as possible.***
4. ***For CNS adverse event indicative of encephalopathy, follow-up will be perform by Intensive Monitoring Program***

APPENDIX 2	The central laboratory will receive and store all shipped samples and will distribute plasma samples to the analytical facilities for analysis of total bismuth ~~**every 20 patients (*i.e.* 40 tubes of plasma).**~~ The TMB metabolite concentration determination will be determined once bismuth concentration is known.

APPENDIX 3	APPENDIX 3 – CENTRAL NERVOUS SYSTEM ADVERSE EVENTS OF INTEREST In order to select the appropriate terms, the original Standardized MedDRA Query (MedDRA ~~13.1~~ ***15.1***SMQ Noninfectious encephalopathy/delirium (20000133)) was revised to specifically address the bismuth encephalopathy and include signs and symptoms that are specific to this risk. Preferred Terms (broad scope): Abnormal behavior; Agitation; ***Agraphia; Alexia***; Altered state of consciousness; Amnesia; Anal sphincter atony; Apathy; Ataxia; Bladder sphincter atony; Cerebellar ataxia; Cerebellar syndrome; Clonic convulsion; Coma; Coma scale abnormal; Complex partial seizures; Confusional state; Convulsion; Convulsions local; Coordination abnormal; Delirium; Depressed level of consciousness; Disturbance in attention; Dysarthria; Dysgraphia; Dyspraxia; ***Faecal incontinence***; Gait apraxia; Gait disturbance; Generalised non-convulsive epilepsy; Grand mal convulsion; Hallucination; Hallucination, auditory; Hallucination, gustatory; Hallucination, olfactory; Hallucination, synaesthetic; Hallucination, tactile; Hallucination, visual; Hallucinations, mixed; Hypersomnia; *Hyporesponsive to stimuli*; Illogical thinking; ***Incontinence*** ; Judgement impaired; Lethargy; Listless; Loss of consciousness; Memory impairment; Mental impairment; ***Mental status changes***; Mood altered; Myoclonus; Paresis anal sphincter; Partial seizures; Partial seizures with secondary generalization; Personality change; Personality disorder; Psychomotor seizures; Restlessness; Simple partial seizures; Sleep disorder; Slow response to stimuli; Sluggishness; Somnolence; Speech disorder; Stupor; Thinking abnormal; Tonic convulsion; Tremor; Unresponsive to stimuli; ***Urinary incontinence***.

AMENDMENT NO. 3

The table below describes the changes introduced in this amendment. The left column identifies the section where the change was made and the right column describes the change introduced. Apart from the changes described in the table below, this amendment includes the following:

- Correction a few typographic errors in the protocol.

Sections	Text that was deleted (~~**deleted**~~) or added (***added***) from the previous amended protocol dated 24 MAY 2013
SECTION 13	**7.3 SUBJECT INFORMATION AND INFORMED CONSENT** Information will be provided to explain, in simple terms, the risks and benefits of the subject's participation in the study, the procedures involved, and other relevant details. Written Informed Consent must be obtained from the subject by the Investigator before the subject enters the study. *The Investigator must adopt a standardized approach for obtaining Informed Consent from each subject.* The following items must be described fully to each subject prior to obtaining consent: • A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed and identification of any procedures which are experimental; • A description of any reasonable foreseeable risks or discomforts to the subject; • A description of any benefits to the subject, which may reasonably be expected from the research; • A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject; • A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the sponsor and the worldwide regulatory agency will inspect the records; • An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject; • A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; • ***A statement that participation in the bio collection is voluntary and that the subject may request the destruction of his/her biological samples;*** • Anticipated circumstance under which the subject's participation may be terminated by the Investigator without regard to the subject's consent; • Any additional costs to the subject that may result from participation in the research;

	• The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject; • A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; • The approximate number of subjects involved in the study; and • Any other country-specific and ICH/GCP requirements.

AMENDMENT NO. 4

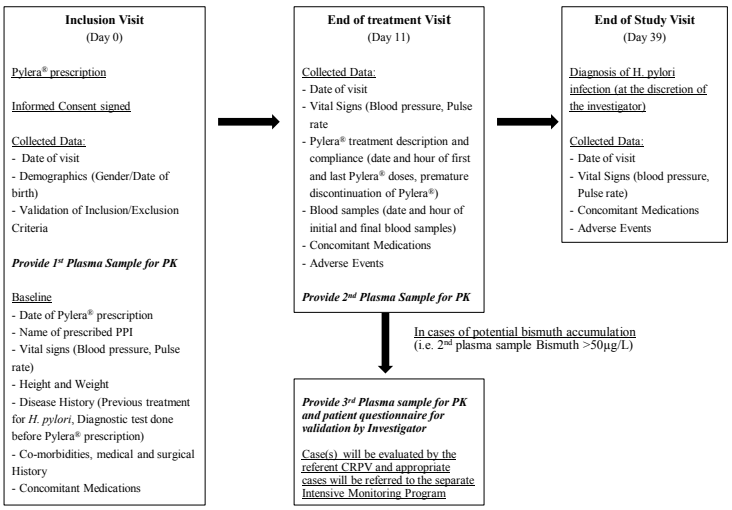
The table below describes the changes introduced in this amendment. The left column identifies the section where the change was made and the right column describes the change introduced. Apart from the changes described in the table below, this amendment includes the following:

- Corrected a few typographic errors in the protocol.

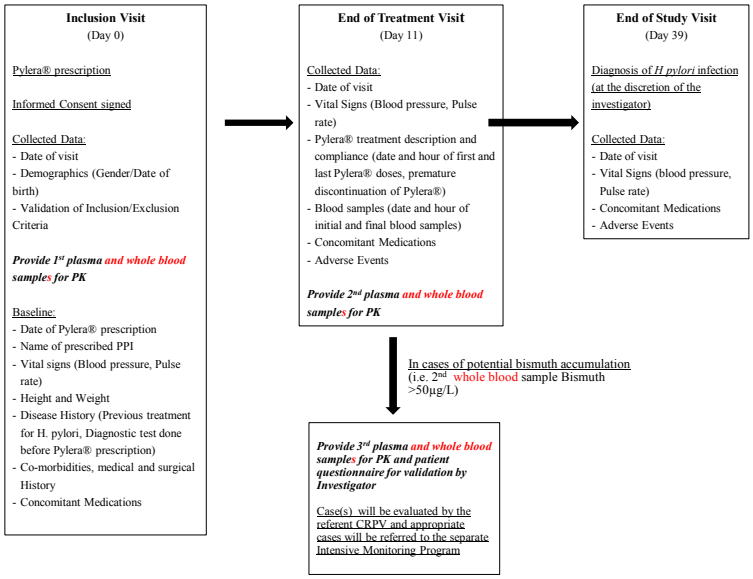
Sections	Text that was deleted (~~**deleted**~~) or added (***added***) from the original protocol dated 24 JUL 2013
PROTOCOL/AMENDMENT APPROVAL PAGE	~~**David Jacobs, MD Senior Director, Clinical Development**~~ ***Dr Robert E. Winkler, Vice President, Global Clinical Development and Operations***
IMPORTANT CONTACTS	The list and contact information involved in the study has been updated. ~~**David Jacobs, MD Senior Director, Clinical Development**~~ ***Dr Robert E. Winkler, Vice President, Global Clinical Development and Operations*** ~~**PD Dr Johannes Lampe, Medical Monitor**~~ ***University of Aberdeen, Dr Eva Krupp, Chemistry Department, Meston Walk, Aberdeen, Scotland, AB24 3UE***
THROUGHOUT THE DOCUMENT	Throughout the document wording has been changed: We add:"… bismuth plasma and ***whole-blood*** concentrations…" We add;"… bismuth ***and TMB*** PK" If accumulation of bismuth is detected (defined as ~~**plasma**~~ ***whole blood*** bismuth concentration exceeding 50µg/L)

SECTION 3

~~**OLD VERSION**~~



NEW VERSION



SECTION 11.7.7	The detection of total bismuth (metal) rather than individual bismuth metabolites permits the detection of all bismuth circulating within the bloodstream irrespective of whatever metabolite form the bismuth atom is found in. ~~**Plasma**~~ ***Whole blood*** TMB will be evaluated using an analytical method derived from Boertz *et al*. (2009)[34] due to the possibility of encephalopathy arising from animal models~~**, but only total plasma bismuth will be the value used to assess accumulation and association with any potential concurrently-reported encephalopathy**~~ For subjects who are already below 50 µg/L on Day 11, no other action will be performed and such subjects will be considered to have reached safe ~~**plasma**~~ ***whole-blood*** levels within an acceptable time.

APPENDIX 2	1) Quantity collected and timeframe: The total volume of blood drawn for bismuth and trimethylbismuth (TMB) pharmacokinetic assessment is anticipated to be ~~**28**~~ ***56*** mL (***8*** ***4*** x 7 mL tubes) over the full study period for each subject. Blood samples will be drawn at two (2) timepoints in the study – one blood draw (amounting to ~~**2**~~ ***4*** tubes, 7 ml each) will be done prior to the start of treatment with Pylera® plus PPI (presumed to be omeprazole) (Inclusion Visit), and a second blood draw sample (amounting to ~~**2**~~ ***4*** tubes, 7 ml each) the day after the end of treatment with Pylera® plus PPI (EOT Visit). The date and time of the two blood samplings will be recorded and reported for each subject. The collection tubes will be shielded from light to minimize photo-degradation and frozen at -20°C before transport for measurement of bismuth and TMB concentration. 2) Type of tubes Blood samples will be obtained from an antecubital vein using two types of tubes: - For bismuth plasma concentration determination: coded EDTA K2 Vacutainers ***tubes or equivalent*** (~~**2**~~ ***1*** x 7 mL tube), - ***For bismuth whole-blood concentration determination: coded sodium citrate-coated Vacutainer tubes or equivalent (1 x 7 mL tube).*** - For TMB whole-blood concentration determination: coded sodium citrate-coated Vacutainer tubes or equivalent (2 x 7 mL tubes). 3) Processing Processing of ~~**two**~~ ***one*** (~~**2**~~ ***1***) blood sample~~**s**~~ per patient for bismuth plasma concentration determination: Following collection, each 7 mL EDTA tube will be centrifuged at 4ºC and 1500 g for 10 minutes; the resulting plasma will be extracted and divided into even numbers of opaque polypropylene snap-cap tubes (minimum two tubes) and frozen at a minimum of -20°C until shipment to the central laboratory for analysis of bismuth plasma concentrations.

APPENDIX 2	***Processing of one (1) blood sample per patient for bismuth whole-blood concentration determination:*** ***The 1 x 7 mL sample will be drawn on citrate-coated tubes not centrifuged, protected from light and frozen at -20°C before transport for whole-blood measurement of bismuth.*** Processing of two (2) blood samples per patient for TMB whole-blood concentration determination: The 2 x 7 mL samples will be drawn on citrate-coated tubes not centrifuged, protected from light and frozen at -20°C before transport for whole-blood measurement of TMB. 4) Transport and concentration determination All sample tubes will be labeled with the study identification number, subject identifier, and time of sampling. Samples will be stored in an opaque box and frozen at a minimum of -20°C until shipment to the central laboratory. Transfer to the central laboratory will be done by an approved transporter under frozen conditions and with samples being shielded from exposure to light. The central laboratory will receive and store all shipped samples and will distribute plasma ***and whole-blood*** samples to the analytical facilities for analysis of total bismuth. The TMB metabolite concentration determination will be determined once bismuth concentration is known. 5) Additional third blood sample This sampling and processing procedure will also be used only if a subject is requested to return to provide a third confirmatory plasma ***and whole-blood*** sample for bismuth analysis in case of clinical symptoms indicative of bismuth-related neurological adverse events or bismuth accumulation at the EOT Visit (total bismuth in ~~**plasma**~~ ***whole blood*** > 50 mg/L).