Protocol – PYR-12-01

PHARE Study

An observational multicenter study on Antibiotic *RE*sistance of *H*elicobacter *P*ylori in France

SPONSOR
Aptalis Pharma Canada, Inc
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PAGE DE SIGNATURE DU PROTOCOLE
PROTOCOL SIGNATURE PAGE

Protocol – PYR-12-01

Etude PHARE
PHARE Study

Etude observationnelle multicentrique de la REsistance de *Helicobacter Pylori* aux Antibiotiques en France
An observational multicenter study on Antibiotic REsistance of Helicobacter Pylori in France

Approuvé par
Approved by :

[redacted]

Personne Qualifiée en matière de Pharmacovigilance au niveau EEE

EEA Qualified Person for Pharmacovigilance

Optum au nom de Aptalis Pharma

Optum on behalf of Aptalis Pharma

[redacted]

Le soussigné a révisé le protocole et est d'accord avec son contenu
The undersigned reviewed the protocol and agrees to its contents

[redacted]

Date (jj/mmm/aaaa)

Date (dd/mmm/yyyy)

INFORMATION

Title	PHARE study: « An observational multicenter study on antibiotic resistance of *Helicobacter pylori* in France »
Protocol Identification version number	Version 5.0
Date of last version of protocol	04/17/2014
EU PAS register number	ENCEPP/SDPP/4110
Active product	Not applicable
Study product	Not applicable
Product reference	Not applicable
Process number	Not applicable
Study authorization holder(s)	Aptalis Pharma SAS
"joint" PASS (Post Authorization Safety Study)	Yes
Research question and objectives	**Research question** This study is intended to address a regulatory requirement for the surveillance of *Helicobacter pylori* susceptibility to antibiotics following the marketing authorization of PYLERA® (bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride) in France. **Primary objective** • To assess the resistance rate in clinical isolates of *Helicobacter pylori* to antibiotics (clarithromycin, levofloxacin, tetracycline, rifamycin, amoxicillin and metronidazole). **Secondary objectives** • To monitor the evolution of strain resistance to antibiotics over the 5 year period following the commercial launch of PYLERA®. • To evaluate the impact of evolution of strain resistance to antibiotics on the efficacy to PYLERA® treatment.
Countries covered by the study	France metropolitan (i.e., France excluding overseas territories)
Author	[redacted]

	[redacted]
Marketing Authorization Holder (MAH)	Aptalis Pharma SAS
MAH contact	[redacted]

1 TABLE OF CONTENT

2 TABLE OF ABBREVIATIONS

ATB(s)	Antibiotic(s)
[redacted]	[redacted]
CNIL	National Commission for Computing and Liberties
CNOM	National Council of the College of Physicians
CRA	Clinical Research Associate
CPP	Committee for Protection of Persons
e-CRF	Electronic Case Report Form
E-test	Epsilometer test
GCP	Good Clinical Practice
H. pylori	*Helicobacter pylori*
MIC	Minimum Inhibitory Concentration
NE	North East
NW	North West
PCR	Polymerase Chain Reaction
PPI	Proton Pump Inhibitor
SE	South East
SW	South West
[redacted]	[redacted]

3 RESPONSIBLE PARTIES

3.1 SPONSOR

Aptalis Pharma Canada, Inc. is located at 597 Laurier Boulevard, Mont St-Hilaire, QUEBEC, J3H 6C4, CANADA and is the sponsor of this study. Aptalis Pharma SAS is the Marketing Authorization holder of PYLERA® and the European representative of the sponsor for the study.

This study is intended to address a regulatory requirement for the surveillance of *Helicobacter pylori* (*H. pylori)* susceptibility to antibiotics following the marketing authorization of PYLERA® (bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride) in France.

This observational study is entitled: «An observational multicenter study on antibiotic resistance of *Helicobacter pylori* in France».

3.2 EXPERT SCIENTIST

An expert scientist has been named as part of this observational study, [redacted]

3.3 LOGISTIC AND ANALYSIS

[redacted] a company specialized in observational studies, is contracted by Aptalis Pharma Canada Inc. to perform in its name and on its behalf, certain clinical services related to the implementation and conduct of the study.

4 ABSTRACT

Title	**An observational multicenter study on antibiotic resistance of *Helicobacter pylori* in France** Study requested by ANSM ("Agence Nationale de Sécurité du Médicament et des produits de santé"- French Health Authorities) as part of the Risk Management Plan for PYLERA® in France Name of the Study : PHARE Version : 5.0 Date : 04/17/2014 Principal Investigator : [redacted]
Rationale and background	Observational multicenter study to be conducted in France, with subjects having scheduled one consultation with their gastroenterologist as part of their regular follow up for an endoscopy with biopsies (antral and fundic) to look for infection by *Helicobacter pylori* and to test the resistance of this bacterium to antibiotics. This study is non-interventional. It is conducted according to the usual medical practice in accordance with the current recommendations and does not impose additional diagnostic approaches or therapeutics strategies.
Research question and objectives	**Research question** This study is intended to address a regulatory requirement for the surveillance of *Helicobacter pylori* susceptibility to antibiotics following the marketing authorization of PYLERA® (bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride) in France. **Primary objective** • To assess the resistance rate in clinical isolates of *Helicobacter pylori* to antibiotics (clarithromycin, levofloxacin, tetracycline, rifamycin, amoxicillin and metronidazole). **Secondary objectives** • To monitor the evolution of strain resistance to antibiotics over the 5-year period following the commercial launch of PYLERA®. • To evaluate the impact of evolution of strain resistance to antibiotics on the efficacy to PYLERA® treatment.
Study design	This is an observational, multicenter study in France.

Population	Participating gastroenterologists will include subjects, based on inclusion criteria, on one specific day per month. **Inclusion criteria** • Subjects 18 years of age and older • Subjects with a scheduled or planned endoscopy at one of the centers involved in the study • Subjects with a pathology potentially associated with an infection by *Helicobacter pylori* or subject with failure to a previous treatment for eradication • Subjects with a signed information leaflet
Variables	Gastroenterologists will collect the biopsies in accordance with the center's usual practices. The required number of biopsies will be collected for the usual anatomopathology evaluation by the center and 2 additional biopsies (1 antral and 1 fundic) will be collected for resistance testing in the context of the study. Safety variables: Not applicable.
Data sources	Data to be collected : • Endoscopy date and sample collection time • Sociodemographic Data: Age, gender, country of birth, current place of residence, education level • Reason(s) for consultation: Subject's symptoms during the visit (epigastric pain, other signs of dyspepsia, anemia, others) • Use of antibiotic(s) in the 30 days prior to the endoscopy including name, duration and end date • Use of Proton Pump Inhibitor (PPI) in the 7 days prior to the endoscopy including name duration and end date • History of *Helicobacter pylori* infection: previous eradication attempts including number of attempt(s), nature and duration of eradication attempt(s), such as the following: - Bismuth quadruple therapy : PPI (omeprazole or other name, and dosage) + PYLERA® (bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride) (10 days) - Triple therapy : PPI + amoxicillin + clarithromycin (7, 10, or 14 days) - Triple therapy : PPI + amoxicillin + metronidazole (7, 10, or 14 days) - Sequential treatment : PPI + amoxicillin (5 days) followed by PPI + clarithromycin + metronidazole (5 days) - PPI + amoxicillin + levofloxacin (10 days) - PPI + amoxicillin + rifabutin (10 days) - Others • Biopsies for bacteriology: localization (antral – fundic) and number • Results of endoscopy: rashes, superficial erosion, ulcers, esophageal diseases, others • Resistance results from central laboratory
Study size	A representative sample of 100 (n=100) gastroenterologists, distributed across 5

	regions of France (North East, North West, South East, South West, Paris area) will be randomly selected to participate in the study. Based on the French population, approximately 23 gastroenterologists will be selected in North East, 23 in North West, 24 in South East, 11 in South West, and 19 in the Paris area. Up to 1000 subjects are expected to be recruited in each collection period. Subject recruitment will be conducted over three separate periods: collection year 1 (1st trimester 2014 to 1st trimester 2015), collection year 2 (1st trimester 2016 to 1st trimester 2017) and collection year 3 (1st trimester 2018 to 1st trimester 2019). Up to 3000 subjects are expected to participate in the study over 5 years.
Data analysis	The resistance of *Helicobacter pylori* to six different antibiotics will be determined by agar diffusion using two different tests: disk diffusion for tetracycline, rifampicin (for rifamycin resistance), and levofloxacin, and Epsilometer test (E-tests) for clarithromycin, metronidazole and amoxicillin. Real time PCR for molecular characterization of resistance mutations associated to clarithromycin resistance will be performed on a subset of strains.
Milestones	• First period of inclusion, collection year 1: 1st trimester 2014 to 1st trimester 2015 • Interim report for collection year 1: 2nd trimester 2015 • Second period of inclusion, collection year 2: 1st trimester 2016 to 1st trimester 2017 • Interim report for collection year 2: 2nd trimester 2017 • Third period of inclusion, collection year 3: 1st trimester 2018 to 1st trimester 2019 • Closure of the database: 2nd trimester 2019 • Final data analysis: 2nd trimester 2019 • Final clinical study report: 3rd trimester 2019

5 AMENDMENTS AND UPDATES

Any substantial changes, other than strictly administrative changes that do not affect subject management, subject safety, clinical procedures, or outcomes assessment will be made as formal amendments to the protocol and will be submitted to appropriate regulatory authorities for review and then distributed to each participating center.

Any change or addition to this protocol requires a written protocol amendment that must be approved by the sponsor 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 appropriate regulatory authorities.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator (gastroenterologist) or by the sponsor in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons the sponsor should be notified within 10 working days. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or regulatory authorities approval, but the regulatory authorities must be kept informed of such administrative changes.

Examples of administrative changes not requiring formal protocol amendments and that can be treated as administrative amendments include changes in the staff used to monitor the study.

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 the medical monitor and will require prior approval. Any unforeseen changes in study conduct will be recorded in the Clinical Study Report (CSR).

6 MILESTONES

Tasks	Estimated date
Beginning of data collection (first subject first visit) for collection year 1	1st trimester 2014
End of data collection for collection year 1	1st trimester 2015
Interim report for collection year 1	2nd trimester 2015
Beginning of data collection for collection year 2	1st trimester 2016
End of data collection for collection year 2	1st trimester 2017
Interim report for collection year 2	2nd trimester 2017
Beginning of data collection for collection year 3	1st trimester 2018
End of data collection (last subject last visit) for collection year 3	1st trimester 2019
Closure of the database	2nd trimester 2019
Final data analysis	2nd trimester 2019
Final clinical study report	3rd trimester 2019

7 RATIONALE AND BACKGROUND

H. pylori is a Gram-negative bacterium, which is spiral-shaped and possesses flagella that confer mobility. It is only found in the antrum, fundus and pylorus of the stomach of humans[1].

H. pylori infection is widespread in the world and infects about 50% of the world population, although there are large geographical differences [2]. Its prevalence is > 90% in Asia, Latin America and other third-world countries, 50 to 70% in Eastern Europe and 30% in Western countries [3].

In France, 20 to 50% of adults are infected by *H. pylori,* depending on their age, and will retain this bacterium unless it is proactively eradicated [4]. Currently, half of the subjects over 60 years host the bacterium in their stomach [5].

Infection might be favored by poor hygiene, poor socio-economic status, as well as the degree of use of ATBs [6]. Infection is always accompanied by inflammation [7].

Infection with *H. pylori* can manifest itself by acute abdominal pain, although in most cases it does not cause pain or other signs (80% of the cases) [8]. The diagnosis of *H. pylori* infection can be established based on different methods: identification of antibodies for *H. pylori* by blood test, testing for the presence of the bacterium in stools or performing a breath test based on the ability of *H. pylori* to metabolize urea into ammonia and carbon dioxide [9,10]. In addition, gastric endoscopy allows the gastroenterologist to collect tissue samples from the stomach in order to directly identify the presence of *H. pylori* [11].

If *H. pylori* infection is not treated, the human immune system is not able to eradicate this bacterium. As a consequence, it can asymptomatically persist through life [12] or develop into severe gastro-duodenal pathologies such as duodenal ulcer, gastric lymphoma (of the Mucosa-Associated Lymphoid Tissue: MALT) or cancer of the stomach [13].

Treatment of *H. pylori* infection significantly reduces the risk of gastric ulcer and improves healing of the ulcer. In case of uncomplicated dyspepsia, it improves symptoms [14]. Additionally, it might also reduce the risk of developing stomach cancer when precancerous lesions exist [15].

There are several international guidelines on the management of *Helicobacter* [16,17]. In Europe, the most important were issued at the Maastricht Consensus Conferences [18,19,20,21].

Combination therapies are the standard therapies for the eradication of *H. pylori* in Europe. Several different combination therapies are available. A typical duration of treatment is between one and two weeks [22]. The *H. pylori* infection can be classically treated with a combination of two ATBs with a Proton Pump Inhibitor (PPI) to neutralize gastric acidity [23].

- amoxicillin + clarithromycin + PPI
- amoxicillin + metronidazole + PPI
- metronidazole + tetracycline + PPI
- metronidazole + clarithromycin + PPI

The combination of amoxicillin with levofloxacin or with rifabutin also has good efficacy for the eradication of *H. pylori*. However, these ATBs should be used as second-line therapies[24].

Sequential therapies for the eradication of *H. pylori* infections have been proposed over the recent years [25]. They are characterized by two successive periods, the first combining a PPI with amoxicillin (5 days) and the second with a triple therapy of PPI + clarithromycin + metronidazole. This approach seems to be more effective, but is more complex than the standard treatment. Data on the sequential treatment approach mainly comes from Italy, and must be validated before giving rise to systematic recommendations [26].

In countries where it is available, the quadruple bismuth therapy of PPI (omeprazole) + PYLERA® (bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride), has been proposed as first-line treatment [27]. This quadruple therapy has been available in the U.S. since 2007 [28,29] and has obtained authorization to be placed on the European market via a decentralized procedure. PYLERA® has been available in France since April 10, 2013.

ATB resistance is the main factor of treatment failure to eradicate *H. pylori* [30]. Recommended therapeutic strategies must take into account the national prevalence of resistance to ATBs. Above a 15% resistance threshold, an ATB is not recommended to be used without testing the resistance of the strain . Laboratory tests (antibiogram [31], or molecular test [32]) that predict resistance and guide selection of the most suitable ATB are necessary before treatment is implemented.

The number of *H. pylori* strains that are resistant to clarithromycin have significantly increased over recent years in Europe (resistance rate > 20%), and the overall efficiency of the standard first-line therapies does not exceed 60 to 70%. This led to the establishment of the Consensus Maastricht Treatment Protocols.

In France, the issue of *H. pylori* resistance to ATBs was the subject of several studies in recent years. One of these studies examined 530 *H. pylori* strains collected between 2004 and 2007 in Paris and Poitiers [33] and determined resistance to different ATBs by an Epsilometer test (E-test), as well as by Scorpion-PCR (Polymerase Chain Reaction) for specifying the determinant(s) of clarithromycin resistance. Of these 530 strains, 138 (26%) were resistant to clarithromycin, 324 (61%) to metronidazole and 70 (13.2%) to fluoroquinolones. One strain was resistant to rifampicin, whereas no resistance to amoxicillin or tetracycline was detected. The prevalence of resistance was higher in strains derived from subjects who had already received eradication therapy (secondary resistance) compared to strains from subjects who were not previously treated (primary resistance): 68% vs 19.1% for clarithromycin, 53.3% vs 13.2% for clarithromycin and metronidazole combined, and 20% vs 12% for fluoroquinolones. This study showed that, unlike clarithromycin or metronidazole for which the level of resistance remained stable over the study period, a significant increase in resistance to fluoroquinolones was observed: 7.3% for 2004-2005 vs. 14.1% for the period 2006-2007.

PHARE study

This observational, national, multicenter 5-year study on *H. pylori* resistance to ATBs was requested by the ANSM ("Agence Nationale de Sécurité du Médicament et des produits de santé"- French Health Authorities) as part of the European Risk Management Plan for PYLERA®. It is intended to address the French regulatory agency requirements for the surveillance over 5 years of *H. pylori* resistance to ATBs following the marketing authorization of PYLERA® in France.

The resistance of *H. pylori* to six different ATBs will be determined for those ATBs approved for the treatment of *H. pylori* infection in France (clarithromycin, levofloxacin, tetracycline, rifamycin, amoxicillin and metronidazole). Bismuth or Bismuth subcitrate potassium resistance is not expected [34].

Given the mechanism of development of ATB resistance in *H. pylori*, i.e., point mutations, there is a slow but progressive increase in resistance due to the selection pressure. The planned surveillance on years 1, 3, and 5, instead of yearly, is thus a suitable frequency for this study.

8 OBJECTIVES

Objectives of the study are:

Primary objective:

- To assess the resistance rate in clinical isolates of *H. pylori* to ATBs (clarithromycin, levofloxacin, tetracycline, rifamycin, amoxicillin, and metronidazole).

Secondary objectives:

- To monitor the evolution of strain resistance to antibiotics over the 5-year period following the commercial launch of PYLERA®.
- To evaluate the impact of evolution of strain resistance to antibiotics on the efficacy to PYLERA® treatment.

This study will be performed after the launch of PYLERA® in France.

9 METHODS OF RESEARCH

9.1 STUDY DESIGN

This study is an observational multicenter study on the resistance of *H. pylori* to six ATBs: clarithromycin, levofloxacin, tetracycline, rifamycin, amoxicillin and metronidazole. This study is to be conducted exclusively in metropolitan France using a representative sample of 100 (n=100) gastroenterologists distributed in 5 regions of France: North East (NE), North West (NW), South East (SE), South West (SW), and Paris area. These gastroenterologists will be randomly selected to participate in the study.

Subjects will be recruited over three separate periods: collection year 1 (1st trimester 2014 to 1st trimester 2015), collection year 2 (1st trimester 2016 to 1st trimester 2017) and collection year 3 (1st trimester 2018 to 1st trimester 2019). Up to 3000 subjects are expected to participate in the study over 5 years. The first subject first visit is planned for February 2014 and the last subject last visit for January 2019.

The participation of a subject in the study will last 1 visit, which will take place during the scheduled endoscopy with biopsies by the gastroenterologist as part of a regular follow up.

Gastroenterologists will collect the biopsies in accordance with the center's usual practices. The required number of biopsies will be collected for the usual anatomopathology evaluation by the center and 2 additional biopsies (1 antral and 1 fundic) will be collected for resistance testing in the context of this study.

Biopsies collected by all gastroenterologists will be sent to [redacted] laboratory of bacteriology where the detection of *H. pylori* and the resistance to ATBs will be determined.

9.2 PARAMETERS

This is an observational, multicenter study to be conducted in metropolitan France. The study will be conducted with an expected 100 gastroenterologists. Up to 1000 subjects will be recruited per collection year:

- Collection year 1: 1st trimester 2014 to 1st trimester 2015
- Collection year 2: 1st trimester 2016 to 1st trimester 2017
- Collection year 3: 1st trimester 2018 to 1st trimester 2019

Periods of inclusion (collection year) can be reduced if the subject recruitment is faster, but each collection year will start in its 1st trimester and will end at the latest on the 1st trimester of the following year.

Up to 3000 subjects will be recruited over 5 years.

9.2.1 Gastroenterologist recruitment

Gastroenterologists will be randomly selected from an exhaustive database of gastroenterologists working in France, either in hospitals or in private office.

As there will be some refusals to participate in the study, the number of gastroenterologists initially selected from the database will be 3 times larger than the number required, thus, about 300 gastroenterologists will be randomly selected in 5 regions of France defined as NE, NW, SE, SW and Paris area.

The random selection will aim to balance the number of gastroenterologists by region based on the distribution of the French population. Based on the French population, approximately 23 gastroenterologists will be selected in NE, 23 in NW, 24 in SE, 11 in SW, and 19 in the Paris area.

Gastroenterologists will be contacted by mail or e-mail [redacted] and will be provided with the study synopsis, and a reply coupon.

The goal is to receive completed reply coupons from 125 interested gastroenterologists. With an expected 20% lost to follow-up, the aim is to obtain fully executed financial agreement from at least 100 gastroenterologists.

9.2.2 Study Implementation

Gastroenterologists who agree to participate in the study will be contacted [redacted] to establish a financial agreement. Each gastroenterologist will sign three copies of the financial agreement and return one copy [redacted] and one to his/her Departmental Council of the College of Physicians (CDOM).

At the beginning of this observational study, all study documents (e.g., protocol, guidelines for filling out the electronic case report form (e-CRF), and regulatory documents) will be made available to the gastroenterologists [redacted] on a secured and protected website. Gastroenterologists involved in the study can access the website through their own login and personal password.

A Clinical Research Associate (CRA) will contact gastroenterologists in their centers for a study initiation visit (implementation of the study) which will be done remotely using telephone and web conference.

A center will be considered ready to enroll subjects when:

1. The financial agreement has been fully executed by all parties and returned [redacted], and
2. The study initiation remote visit has been completed.

9.2.3 Subjects recruitment

In agreement with the observational nature of this study, there is no change in the usual medical practice of the gastroenterologist. The only exception is during the endoscopy, in addition to the biopsies to be collected per the usual practice, two additional biopsies (antral

and fundic) will be collected. Any procedures required by the study will be done in accordance with the current recommendations and will not impose additional therapeutic or diagnostic procedures.

Before including a subject in the study, the gastroenterologist must provide the subject with all the relevant study information, including the information leaflet (Appendix 1). The information leaflet must be signed by the subject before being included in the study in order to document their agreement to participate.

Over a period of 5 years, participating gastroenterologists will include up to 20 subjects for each collection year (60 subjects overall) that meet the inclusion criteria. To aid logistical management of the study (e.g., transport of biopsies to central bacteriology laboratory) each gastroenterologist will have 1 pre-identified day per month to include subjects (except Fridays).

9.2.4 Visit procedures

Before including a subject in the study, the information leaflet will be provided to the subject and the study will be explained in sufficient detail to allow for the subject to make an informed decision to participate. If the subject understands the requirements of the study and agrees to participate, the subject will sign the information leaflet. Following signature of the information leaflet, each subject will be enrolled in the study by assignment of a unique sequential enrollment number, composed of the center unique number followed by the subject sequential number, first letter of the subject last name and first letter of the subject first name.

The following eligibility criteria will be verified:

- Inclusion criteria:
  - Subjects 18 years of age and older
  - Subjects with scheduled or planned endoscopy at one of the centers involved in the study
  - Subjects with a pathology potentially associated with an infection by *H. pylori* or subjects with failure to a previous treatment for eradication
  - Subjects with a signed information leaflet

The two additional biopsies (antral and fundic) collected for this study will be immediately stored at 4°C in a tube with special medium "Portagerm pylori" and will be sent the same day to [redacted] laboratory by an identified specialized transport company. At the time of transport, the tube will be placed into a packaging for refrigerated shipment. Prior to study start, centers will be provided with detailed instructions on how to contact the transport company.

At the visit:

The following information will be collected during the subject visit and recorded in the e-CRF:

- Subject identification (center number, subject number, first letter of subject last name and first letter of the subject first name)
- Date of endoscopy and sample collection time

- Confirmation of inclusion criteria:
  - Subject 18 years of age or older
  - Subject has a scheduled or planned endoscopy at one of the centers involved in the study
  - Subject has a pathology potentially associated with an infection by *H. pylori* or subject with failure to a treatment for eradication
  - Subject has a signed information leaflet
- Sociodemographics data:
  - Age
  - Gender
  - Country of birth
  - Current place of residence
  - Education level
- Reason(s) for consultation:
  - Epigastric pain
  - Other signs of dyspepsia
  - Anemia
  - Others
- Use of ATB(s) in the 30 days prior to the endoscopy
  - Name
  - Duration
  - End date
- Use of PPI in the 7 days prior to the endoscopy
  - Name
  - Duration
  - End date
- History of *H. pylori* infection :
  Previous eradication attempts, including number of attempt(s), nature and duration of eradication attempt(s) among the following:
  - Bismuth quadruple therapy : PPI (omeprazole or other name and dosage) + PYLERA® (bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride) (10 days)
  - Triple therapy : PPI + amoxicillin + clarithromycin (7, 10 or 14 days)
  - Triple therapy : PPI + amoxicillin + metronidazole (7, 10 or 14 days)
  - Sequential treatment : PPI + amoxicillin (5 days) followed by PPI + clarithromycin + metronidazole (5 days)
  - PPI + amoxicillin + levofloxacin (10 days)
  - PPI + amoxicillin + rifabutin (10 days)
  - Others
- Biopsies for bacteriology:
  - Localization and number of biopsies
- Results of endoscopy:
  - Rashes
  - Superficial erosion
  - Ulcers
  - Esophageal diseases
  - Others

This study does not require a follow up visit; all data will be collected on the day of the endoscopy.

9.2.5 Monitoring the study

The centralized monitoring will be provided [redacted] and will mainly be done remotely using telephone. CRAs will also provide support to gastroenterologists via a phone line service during regular business hours. Queries on incomplete data for e-CRFs will also be sent via the database if needed.

On-site monitoring visits are also planned during the course of the study. On-site monitoring will be carried out for a sample of gastroenterologists with ten percent (10%) of centers, across all regions, planned to be visited. For on-site monitoring, the 10% of centers will be randomly selected among centers which have at least one subject included in the study.

On-site monitoring visits are scheduled as follow:

- 4 monitoring visits spread out during the first collection year (2 in 2nd trimester 2014, 1 in 3rd trimester 2014 and 1 in 4th trimester 2014)
- 3 monitoring visits spread out during the second collection year (2nd trimester 2016, 3rd trimester 2016 and 4th trimester 2016)
- 3 monitoring visits spread out during the third collection year (2nd trimester 2018, 3rd trimester 2018 and 4th trimester 2018)

During these on-site visits, the CRA will verify, among other things, the compliance with inclusion criteria and the completeness of collected data, ensuring comprehensive and complete documentation from data source.

By agreeing to participate to this study, gastroenterologists also agree to receive phone calls in case of missing data or in case of major inconsistencies found in the e-CRFs.

9.3 VARIABLES

The resistance of *H. pylori* to six different ATBs will be determined by agar diffusion using two different tests: disk diffusion for tetracycline, rifampicin (for rifamycin), and levofloxacin, and E-tests for clarithromycin, metronidazole, and amoxicillin.

All biopsies sent by gastroenterologists will be cultured for 8 days in order to detect the presence of *H. pylori*.

- Negative result : Absence of *H. pylori*
- Positive result : Presence of *H. pylori*

} These results will be used to calculate the percentage of subjects infected with *H. pylori*.

For positive results (presence of *H. pylori*), the resistance to ATBs will be carried out as follows:

ATBs resistance tests:

- The E-test consists of a predefined gradient of ATB concentration on a plastic strip which when applied to inoculated agar plates and incubated, creates an ellipse of microbial inhibition. The point at which the ellipse meets the strip gives a reading of the Minimum Inhibitory Concentration (MIC) of the tested ATB.
- The disk diffusion test consists of filter-paper disk pre-impregnated with a standard concentration of ATB which is applied to inoculated agar plates and incubated. If the ATB is effective against the bacteria at a certain concentration no colonies will grow. The diameter of the zone of inhibition gives the MIC of the tested antibiotic.

Reading of inoculated plates will be conducted after 3 days incubation. MICs will be measured and reported for the antibiotics tested by E-test and zone sizes for those tested by disk diffusion.

The interpretation criteria of the category of resistance will be determined by the standard phenotypic method according to the recommendations of CA-SFM (Comité de l'Antibiogramme de la Société Française de Microbiologie) *(http://www.sfm.asso.fr)*:

By Disk:

- For tetracycline:
  - Resistant ≤ 17 mm
  - 17 mm < intermediate resistance < 19 mm
  - Sensitive ≥ 19 mm
- For rifampicin (for rifamycin):
  - Resistant ≤ 14 mm
  - 14 mm < intermediate resistance < 19 mm
  - Sensitive ≥ 19 mm
- For levofloxacin:
  - Resistant ≤ 17 mm
  - 17 mm < intermediate resistance < 19 mm
  - Sensitive ≥ 19 mm

By E-test:

- For clarithromycin:
  - Sensitive ≤ 0,25 µg/ml
  - 0,25 µg/ml < intermediate resistance < 0,5 µg/ml
  - Resistant ≥ 0,5 µg/ml
- For metronidazole:
  - Sensitive ≤ 8 µg/ml
  - Resistant > 8 µg/ml
- For amoxicillin:
  - Sensitive ≤ 0,12 µg/ml
  - Resistant > 0,12 µg/ml

Double populations and/or isolated colonies growing inside the inhibition zone will be considered as resistant.

In case of contaminant flora, a sub-culturing of colonies will be performed if necessary and a second test will be performed if colonies are confirmed to be *H. pylori* colonies.

In addition, PCR will be performed on a sub-group of *H. pylori* strains resistant to clarithromycin for the associated molecular characterization of resistance.

The central laboratory will be responsible for sending the results of *H. pylori* infection and the resistance results to the participating centers [redacted].

9.4 DATA SOURCES

To meet the objectives of the study, data collection will be carried out with the help of specific tools developed [redacted].

The data collected during the subject visit will be entered by the gastroenterologists in the e-CRF. For this purpose, each gastroenterologist will receive a unique and confidential login and password to the e-CRF. The e-CRF developed for the study consists of two kinds of questions:

- Questions with answers being single choice among several proposals/propositions
- Multiple choice questions

Most questions will be answered in the format of check boxes with an additional text area available for any clarifications or comments.

The e-CRF will be completed using information gathered from subjects and recorded in their medical records (source documents).

The data produced by the bacteriology laboratory will be transferred [redacted] and the gastroenterologists; [redacted] will then add these data to the relevant e-CRFs.

9.5 STUDY SIZE

Calculation of the number of subjects for the study:

The study aims to evaluate the rate of *H. pylori* resistance to each of the six ATBs with pre-determined precision.

The number of subjects required is determined by the desired accuracy for the observed percentages and the alpha risk. The table below shows that a sample of 1000 subjects representative of the French population (with symptoms of *H. pylori* infection or having had a previous eradication therapy) will allow assessment of resistance level of *H. pylori* to ATBs with an accuracy between ± 3.0% and ± 3.5% for all possible expected percentages from 5% to 50% of subjects included.

This assessment will be done as accurately as possible, using a bilateral confidence interval of 95%.

	Expected Percentage								
Level of precision	5%	10%	15%	20%	30%	35%	40%	45%	50%
± 2,0%	457	865	1225	1537	2017	2185	2305	2377	2401
± 3,0%	203	385	545	683	897	972	1025	1057	**1068**
± 3,5%	149	283	400	502	659	714	753	777	**784**
± 4,0%	115	217	307	385	505	547	577	595	601
± 5,0%	73	139	196	246	323	350	369	381	385

The size of the sample is given by the following formula:

$$n = \frac{\left(z_{1-\alpha/2}\right)^2 \times p \times (1-p)}{i^2}$$ wherein:

- p is the expected percentage of subjects with *H. pylori* that is resistant to at least one of the six ATBs,
- $(1-\alpha)$ is the desired confidence level for the interval and z is the quantile of the standard normal distribution corresponding to the probability $1-\alpha/2$,
- i is the precision that is desired.

9.6 DATA MANAGEMENT

Data management will be the responsibility [redacted] and it will be performed using ORACLE CLINICAL with RDC (Remote Data Capture).

All data will be collected using an integrated Web-based system. The Web-based system will be in adherence with regulations and will consist of an e-CRF to handle data collection. The set-up of the Web-based system will be executed [redacted]. Completion guidelines will be developed to provide guidance to study center personnel on how to record data in the e-CRF.

A detailed Data Validation Plan will be developed to ensure the quality of the data.

The Web-based system will integrate data discrepancy management and resolution with audit trails. The e-CRF will be validated through extensive data checking and query processing capabilities. Capabilities will include generating open queries and routing answers.

Two interim analysis reports are planned (one in the 2nd trimester 2015 and one in the 2nd trimester 2017) as well as a final analysis planned in the 2nd trimester 2019. After validating the data, a review will be conducted with the sponsor before each of the interim analyses and before final database lock. Statistical analyses will be made after the database lock.

Medical history and treatment will be coded if necessary, using:

- MedDRA for medical history
- WHO-Drug for treatment.

9.7 DATA ANALYSIS

The statistical analysis and methods will be detailed in a separate Statistical Analysis Plan (SAP) to be developed and filed before the database lock for the first interim analysis.

Populations Analysis:

All subjects enrolled in the study will be included in the analysis. Tabular summaries and listings will present the data collected from the e-CRF including:

- Sociodemographic data
- Reason for consultation
- Use of ATB(s) in the 30 days prior to the endoscopy
- Use of PPI in the 7 days prior to the endoscopy
- History of *H. pylori* infection (including previous eradication attempts)
- Results of endoscopy
- Presence or absence of *H. Pylori* detected by culture [redacted]
- Results of resistance tests to each of the six ATBs
- Result of PCR when it's performed

The primary endpoint is the resistance rate of *H. pylori* (percentage) to clarithromycin, levofloxacin, tetracycline, rifamycin, amoxicillin and metronidazole. The rate of *H. pylori* resistance to each of the six ATB will be calculated and the percentage of subject with *H. pylori* that is resistant to at least one of these six ATBs will be calculated. The corresponding 95% confidence interval based on the normal distribution will be obtained for each period of data collection in the five regions (NE, NW, SE, SW and the Paris area). Resistance rate of *H. pylori* to each ATB is defined in this study as the percentage of subjects with *H. pylori* that is resistant to the ATB.

In addition, study resistance rate results will be compared to historic results published from previous studies in France.

For secondary endpoints to assess the change in resistance over the 3 collection periods, the results obtained at the different times points will be compared. This comparative analysis will be conducted as follows and will involve comparison of the 5 regions of France:

- The resistance rates of first and second collection years will be compared;

- The resistance rates of second and third collection years will be compared;
- The resistance rates of first and third collection years will be compared.

The analysis will be performed for subjects who had never received treatment for *H. pylori* and for those who have received prior treatment. Among those who have received prior treatment, the subgroup treated with PYLERA® will be especially studied. Evaluation of resistance data in relation to subject's treatment history for *H. Pylori* eradication will be taken into consideration to interpret the impact of the evolution of resistance on PYLERA® treatment efficacy. In addition, post-marketing data available at the time of the report will also be taken into account to interpret the resistance data in relation to PYLERA® treatment.

Statistical Methodology:

First, a descriptive analysis will be conducted on the various parameters of the study:

- Qualitative variables: numbers, percentages, missing values, 95% confidence intervals
- Quantitative variables: mean, standard deviation, missing values, minimum and maximum values, median and quartiles, 95% confidence intervals

In a second step, it is planned to compare the results obtained over the 3 collection periods and with different subgroups of subjects (Subgroups: age, gender, country of birth, current place of residence, education level). The nature of the test used depends on the variable.

- Quantitative Variable: The normality will be assessed first using the Kolmogorov Smirnov test. If normality assumption is met, then analysis of variance will be performed; otherwise, the non-parametric Kruskal-Wallis test will be applied.
- Qualitative Variable: For this type of variable, Fisher's exact or chi-square test will be used.

9.8 QUALITY CONTROL

The sponsor has instituted a Quality Assurance program to ensure that all aspects of the study will be conducted according to Good Clinical Practices (GCPs), and applicable laws and regulations. This may include an audit by the sponsor and/or regulatory agency representative at any time. The gastroenterologist must agree to the audit of study-related records by regulatory agency and/or the sponsor. The gastroenterologist must adhere to these principles, in addition to any applicable or local requirements.

Study Archiving:

The sponsor will comply with all GCP requirements for study archiving. Source documentation with confidential data of subjects must not be archived by the sponsor but must be retained by the gastroenterologist according to local regulations on the protection of personal data.

The gastroenterologist will agree to file documents related to the study in an archive during or after closure of the study. The gastroenterologist must not destroy documents without prior authorization from the sponsor.

The sponsor will retain documentation relating to the study in accordance with appropriate regulations.

The database of the study will be sent to the sponsor and will be archived after finalization of the study report.

9.9 LIMITATIONS OF THE RESEARCH METHODS

An observational study is carried out under real-life conditions without intensive monitoring of data collected. It is therefore possible that the complete data as requested in the protocol will not be available for analysis for all subjects.

9.10 DISCONTINUATION OF THE STUDY

The sponsor may terminate the study for safety or administrative reasons at any time. In such cases, the termination procedures set forth in the individual agreement with the clinical center will be followed.

The sponsor will notify the regulatory authorities where the study is being conducted (no later than 15 calendar days in Europe) regarding the rationale for the termination of the study.

10 PROTECTION OF HUMAN SUBJECTS

The study will be conducted in accordance with GCP and data collection will be based on the requirements of local laws and on Advisory Committee on Information Processing in Research in the field of Health (CCTIRS) and National Commission for Computing and Liberties (CNIL).

10.1 NATIONAL COUNCIL OF THE COLLEGE OF PHYSICIANS (CNOM)

Compensation of gastroenterologists as part of their activity in the study will be provided in accordance with Article L.4113-6 of the code of public health for physicians. Under Article

L.4221-17 of the same code, a statement will be submitted to CNOM. In accordance with Article L.4113-6 an absence of answer from the authority is to be considered a favorable opinion if no response is received within 2 months of submission of the statement.

10.2 NATIONAL COMMISSION FOR COMPUTING AND LIBERTIES (CNIL)

Since personal data from gastroenterologists (e.g., name, gender and age) will be subject to computer processing, the data for all gastroenterologists will be subject to a declaration to the CNIL. Each gastroenterologist has the right to access and correct the data, pursuant to Articles 39 and following the law of 6 January 1978, called "Data Protection Act", as amended by the Act of 6 August 2004. The gastroenterologist will have the right to access the data via the sponsor [redacted] if necessary.

The subjects' data are collected in a strictly anonymous way. No subject name is collected during the course of the study (e-CRF and/or specifications for data collection). Only a subject number is used to ensure traceability of data. This number will be the center number combined with a subject sequential number, the first letter of subject last name and the first letter of the subject first name.

There is no direct connection between the gastroenterologist database (for administrative use, containing gastroenterologist data only) and the study database used to collect subject data (for statistical analysis use).

A request for authorization for the automated processing of personal data with the purpose of establishing an observational study will be lodged with the CNIL.

10.3 COMMITTEE FOR PROTECTION OF PERSONS (CPP)

This study is non-interventional; it does not change the gastroenterologist-subject relationship and does not fall within the scope of biomedical research. Therefore, no written consent is mandatory and a prior request for advice from a CPP is not necessary and will not be done. The sponsor, in collaboration with UCR, has however decided to provide subject with an information leaflet to document each subject's participation agreement.

10.4 ETHICS

The gastroenterologist is bound to confidentiality and privacy about the identity of subjects in accordance with applicable laws.

The gastroenterologist must also ensure compliance with the study protocol procedures and agrees to provide all requested data in an accurate and legible way.

10.5 GASTROENTEROLOGIST-SUBJECT RELATIONSHIP

The gastroenterologist must inform each subject that data collected for this study will be anonymously collected. The gastroenterologist has for this purpose an information leaflet that will be signed by each subject. A copy of the signed information leaflet will be retained in the subject's medical record and a signed copy will be given to each subject.

11 MANAGEMENT AND REPORTS OF ADVERSE EVENTS/ADVERSE REACTIONS

There will be no interventions in addition to normal practice as a result of study participation, so there is no planned collection of study-related adverse events (either product-related or procedure-related).

Gastroenterologists who become aware of an adverse event requiring spontaneous reporting during the subject's participation in the study are encouraged to report the event via their Regional Center for Pharmacovigilance (CRPV).

12 PLAN OF DISTRIBUTION AND COMMUNICATION OF RESULTS

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

The sponsor is committed to ensure that publication of all of its studies result 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). The sponsor is committed to ensuring that authorship for all publications comply with the criteria defined by the ICMJE.

The sponsor has committed to make the PHARE study information available in the EU electronic register of post-authorization studies (EU PAS Register) in accordance with Good Pharmacovigilance Practices Module VIII requirements.

Clinical studies may involve already marketed products and/or investigational products. The sponsor is committed to the timely submission and registration on a public database (e.g.,Clintrials.gov) of summary information concerning all clinical studies that the sponsor is conducting. These clinical studies will involve use of the sponsor's marketed or investigational products. The sponsor is also committed to the timely submission and posting of summary results of all clinical studies conducted in subjects involving the use of the sponsor'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 investigator for this study are set forth in the individual agreements with each clinical site.

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ANNEXE 1: INFORMATION LEAFLET

Madam, Sir,

Your doctor suggested you participate in a vast national, observational study on resistance to antibiotics in the treatment against *Helicobacter pylori* (*H pylori*). This observational study is being paid for and sponsored by Aptalis Pharma Canada, Inc. (the "Sponsor"), who is also manufacturing in France a *H pylori* treatment, PYLERA®. This observational study will be carried out in approximately 100 medical centers located in France and will involve approximately 3000 subjects.

The purpose of this observational study is to collect information to evaluate resistance to antibiotics used to eradicate *H pylori* in France. This observational study will also evaluate the evolution of resistance to antibiotics in the French population over a 5 year period and will evaluate the impact of this resistance evolution on the efficacy of PYLERA® as a treatment for *H pylori*.

This study is termed observational, meaning that no additional examination will be required. This observational study will take place during your usual visit to the doctor and will not necessitate additional visit or medical test.

Your doctor already prescribed an endoscopy with biopsies because he/she suspects a pathology induced by an *H pylori* infection or a failure to the first line of treatment toward *H pylori* eradication. As part of this observational study, your doctor will collect 2 additional samples at the same time he/she collects the usual samples. The number of samples usually collected during a prescribed endoscopy is 4, if you take part in the observational study 2 additional samples will be collected. The 2 additional samples will be collected with the same procedures as the usual samples and will not require any additional medical examination. There is a rare risk of bleeding associated with collection of the usual samples. The additional 2 samples do not induce a new risk, they only slightly increase the already existing risk.

If you agree to participate in this observational study, your doctor will collect your clinical and sociodemographic data (age, place of birth, place of residence, level of education), the reason for your visit, your use of antibiotics in the last 30 days and Proton Pump Inhibitor in the last 7 days and the history of your previous infection by *H pylori*. The results of your endoscopy will also be collected. Following the endoscopy and without waiting for the study results, your doctor will decide on the treatment you should follow. Six weeks later, your doctor will be informed regarding the culture of your 2 additional samples, and whether or not *H pylori* was detected. In case of infection by *H pylori*, he/she will also be informed on the potential resistance of the bacterium to the following antibiotics: clarithromycin, levofloxacin, tetracycline, rifamycin, amoxicillin and metronidazole.

The Sponsor, affiliated companies of Sponsor, their representatives, the clinical research team from the company appointed by Sponsor and representatives of national and international health authorities will be allowed a direct access to your medical file in order to validate the data reported to the monitoring center. These persons will be authorized to examine, analyze and verify all data important for the evaluation by the monitoring center.

However, they will not violate the confidentiality of your medical file, such as specified in the current French laws and regulations.

The 2 additional samples being collected as part of this observational study and their associated testing are being paid for by the Sponsor. However, all of the already planned procedures associated with the standard of care (already prescribed endoscopy and biopsies) will not be paid by the Sponsor.

The study protocol, the information about the subject collected during the visit, as well as information leaflet, have been subjected to the approval of CCTIRS (Advisory Committee on Information Processing Research in the field of Health), which has expressed a favorable opinion on the 05/09/2013, and an authorization request was made to the CNIL (National Commission for Computing and Liberties).

All data registered during this observational study will be collected in a highly confidential way and coded without mention of name and first name in computer files. Records identifying you will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publically available; however, absolute confidentiality cannot be guaranteed. Sponsor has provided the preliminary formalities concerned by the Information and Liberty Acts at the CNIL in application of articles 40-1 and following the law on "Computing and Liberties".

In accordance to the law 78.17 « Computing and Liberties » of 6th January 1978 (chapter V) modified by the law 2004-801 of 6th August 2004 and as well as the recommendations of the CNIL, You benefit from a right of access and rectification of your data, as well as of opposition by notification to your doctor.

Information collected about you in this observational study may need to be sent to companies, entities and individuals located in other countries, including the United States. Therefore, by signing this Information leaflet you hereby expressly grant your consent to the transfer of information collected about you in the course of this observational study to any country in the world for processing, including the United States and other countries that do not have data protection laws as strict as those in force in France.

The results of the observational study may be published in the medical literature or presented at meetings; however, in this case, you will not be identified.

There is no guarantee that you will directly benefit from participating in this observational study. The information obtained from this observational study may contribute to a better understanding of the disease and/or the Sponsor drug, PYLERA®.

In the event you become hurt or sick as a direct result of any properly performed procedure required under the study protocol, your medical expenses will be paid for, provided you have followed the directions of your study doctor/study staff.

You will not lose any of your legal rights if you decide to sign this Information leaflet.

You are of course totally free to accept or not to participate in this observational study, and you will be free to return on your decision without having to justify.

The decision to refuse to participate in the observational study or to withdraw from the observational study at any time will not cause any harm to the care given to you or the quality of your relationship with your doctor.

You will not receive any payment for taking part in this observational study.

You will be given a signed and dated copy of this Information leaflet for your own information.

If you have questions, do not hesitate to ask your doctor.

We thank you sincerely for your participation in this observational study.

Consent statement

I, the subject, agree to participate in the observational study, which has been described to me.

Subject:

Date: _____ (mm/dd/yyyy) Signature: _____

Name (in character): _____

Person obtaining Informed Consent :

Date: _____ (mm/dd/yyyy) Signature: _____

Name (in character): _____