

GlaxoSmithKline

POSTHER

Statistical Analysis Plan

Version: Final version 1.0

Date: 03 nov 2017

**Burden of herpes zoster and postherpetic neuralgia among people  $\geq 50$  years old  
in France**

**STUDY NUMBER: EPI-**

PPD

**ZOSTER-020 BOD FR (201926)**

**STUDY NAME: POSTHER**

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**FINAL STATISTICAL ANALYSIS**

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**LIST OF ABBREVIATIONS AND DEFINITION OF TERMS**

Abbreviation	Definition
ATC	<i>Anatomic and Therapeutical Class</i>
CI	<i>Confidence Interval</i>
CRF	<i>Case Report Form</i>
CRO	<i>Clinical Research Organization</i>
DREES	<i>Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques</i>
EQ-5D-5L	<i>EuroQol 5 dimensions 5 levels</i>
GDP	<i>Gross Domestic Product</i>
GP	<i>General Practitioner</i>
HZ	<i>Herpes Zoster</i>
PHN	<i>Post Herpetic Neuralgia</i>
PRO	<i>Patient Reported Outcomes</i>
Q1	<i>1<sup>st</sup> quartile</i>
Q3	<i>3<sup>rd</sup> quartile</i>
SAP	<i>Statistical Analysis Plan</i>
SD	<i>Standard Deviation</i>
SS	<i>Social Security</i>
ZBPI	<i>Zoster Brief Pain Inventory</i>

## Statistical Analysis Plan

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## DOCUMENT HISTORY

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0.3	06-Oct 2017		Post CS version	PPD (Stat Process)
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1.0	03-Nov-2017		Final version	PPD (Nukléus)

## 1. OVERVIEW AND STUDY PLAN

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical technique to be used to realize the analysis of data for study POSTHER – EPI-ZOSTER-020 BOD FR (201926).

### 1.1 Objectives

The primary objective is to evaluate Herpes Zoster (HZ)-related and Post Herpetic Neuralgia (PHN)-related direct medical costs and indirect costs during a 9 months period (overall, by gender and classes of age) among people  $\geq 50$  years old in France.

Secondary objectives are:

- To describe HZ and PHN pain severity during a 9 months period (overall and by classes of age)
- To evaluate the impact of HZ and PHN on the quality of life of patients during a 9 months period (overall by gender and by classes of age)

## 1.2 Study design

This is an observational, prospective cohort study of patients  $\geq 50$  years old with a Herpes Zoster (HZ) diagnosis, carried out by a French national random sample of community first line practitioners concerned by HZ diagnosis: general practitioners (GPs), dermatologists and ophthalmologists.

Patients  $\geq 50$  years old with a primary HZ diagnosis (no earlier case of HZ) were included in the **HZ cohort** during a one-year inclusion period.

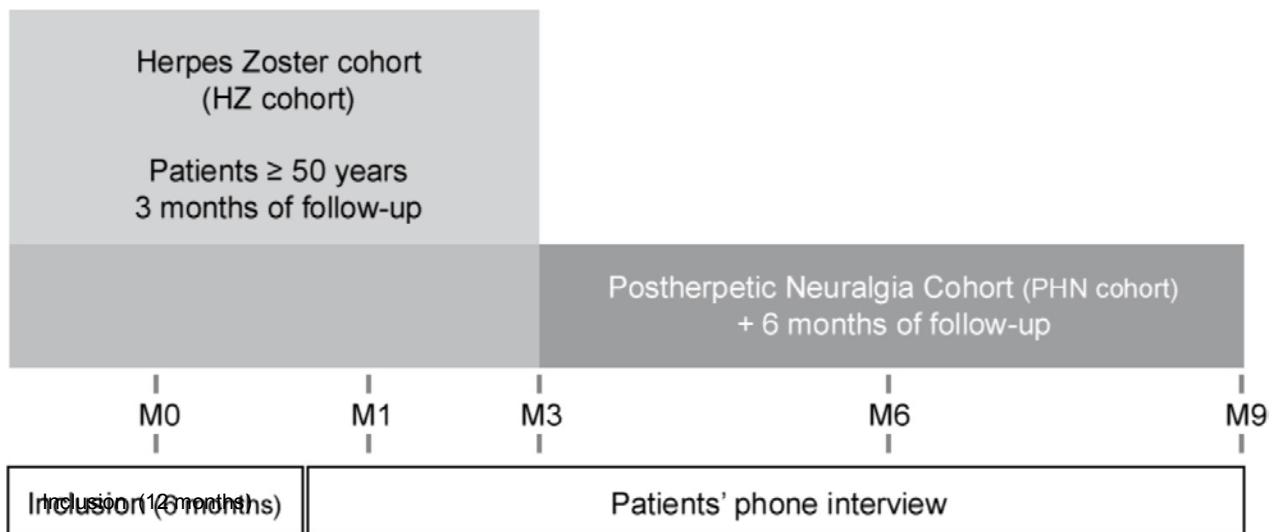
All patients of the HZ cohort presenting Post Herpetic Neuralgia (PHN) 3 months (defined as the presence of HZ-associated severe "worst" pain: pain  $\geq 3$  from ZBPI item "worst pain") after HZ rash onset symptoms were included secondarily in the **PHN cohort**.

Patients of the HZ cohort were followed-up for 3 months using phone interviews with a nurse at 1 month (+/- 3 days) and 3 months (+/- 1 week) after HZ rash onset.

Patients of the PHN cohort were followed up for another 6 months period using phone interviews with a nurse a 6 months (+/- 1 week) and 9 months (+/- 1 week) after HZ rash onset.

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Graph 1: Study Design



### 1.3 Determination of sample size

#### 1.3.1 Subjects

The study was initially designed to include 250 cases of HZ with 40 cases of PHN expected (hypothesis of 16% of PHN at M3).

For quantitative variables, such as costs and utilities, the precision is a function of the variability of the variable. With a sample of 250 subjects, a precision between  $\pm 3.1\%$  and 24.8% is obtained for a standard deviation between  $\frac{1}{4}$  and 2 times the mean. With 40 subjects and still a standard deviation between  $\frac{1}{4}$  and 2 times the mean, a precision of the mean between  $\pm 7.7\%$  and 62.0% is obtained.

**Table 1: Precision of a 95% CI for a continuous variable, taking into account the standard deviation and sample size, according to the normal distribution of the mean**

Sample size (n)	Standard Deviation (SD as % of the mean)					
	1/4	2/4	3/4	1	1,5	2
250	3,1%	6,2%	9,3%	12,4%	18,6%	24,8%
40	7,7%	15,5%	23,2%	31,0%	46,5%	62,0%

$\pm 1,96 \times SD / \sqrt{n}$ , with SD the standard deviation and n the sample size.

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### 1.3.2 *Physicians*

In the study of the General Practitioners' sentinel electronic surveillance network, the average yearly number of cases reported by each GP was 3.31 (95%CI 2.82; 3.80) (Gonzales Chiappe S, 2010).

For the Posther study, it was assumed that GPs and specialists would include at least a mean number of 1 and 2 subjects respectively, for an initial 6 months period. With this hypothesis, a random sample of 170 GPs, 20 dermatologists and 20 ophthalmologists could include 250 cases of HZ.

In cohort studies, some participating physicians are not active, especially with scarce patients such as HZ cases. Assuming a rate of two thirds of active participation, 210 GPs, 30 dermatologists and 30 ophthalmologists should be recruited.

## 1.4 Modifications from the protocol

### 1.4.1 *Physicians' recruitment*

Due to the slowest rate of inclusion of patients than expected, the inclusion period was lengthened from 6 months to 12 months.

For the same reason, the random sample of potential investigators was extended to the list of medical professionals managing HZ provided by the OpenRome organization. Open Rome, thanks to a professionals' ad hoc network pre-positioned, livened up by an independent technical team, is capable of

- mobilizing the actors of health of first appeal around the surveillance of the environment,
- leading at any time investigations of ground, locating factors, exposed people and counting the cases

### 1.4.2 *Number of subjects*

Despite the corrective actions conducted in the patients' recruitment process, the final number of subjects expected to be included in the study is around 100.

With a sample of 100 subjects, a precision between  $\pm 4.9\%$  and 39.2% is obtained for a standard deviation between  $\frac{1}{4}$  and 2 times the mean.

**Table 2: Precision of a 95% CI for a continuous variable, taking into account the standard deviation and a sample size of 100 patients, according to the normal distribution of the mean**

Sample size (n)	Standard Deviation (SD as % of the mean)					
	1/4	2/4	3/4	1	1,5	2
100	4,9%	9,8%	14,7%	19,6%	29,4%	39,2%

$\pm 1,96 \cdot SD / \sqrt{n}$ , with SD the standard deviation and n the sample size.

All the analyses will be performed as initially planned, except when the number of patients in a subgroup of interest is below 5.

## 2. POPULATIONS

### 2.1 Patients' population

To be included in the HZ cohort, patients had to fulfill all the following criteria:

- Patients with a first visit for a diagnosis of HZ and who attend the clinic within two weeks of the start of HZ symptoms (defined as unilateral pain accompanied by a unilateral rash without alternative diagnosis)
- Without any history of previous HZ
- $\geq 50$  years old
- Who agree to participate and signed informed consent
- Able to understand the study, to complete self-administered questionnaires (alone or with the help of a relative) and to answer phone interviews

All patients of the HZ cohort presenting PHN 3 months after onset of the HZ rash onset should be included in the PHN cohort.

PHN was defined as the presence of HZ-associated severe pains:  $\geq 3$  of the ZBPI item "worst pain", completed during the phone interview of the patient at 3 months  $\pm 1$  week.

### 2.2 Patients' analyzable population

Patients included with

- All Inclusion criteria met are selected in the analyzable patients population of the HZ cohort.

Among them, patients with

- An answer  $\geq 3$  at Item 3 of the ZBPI "Please circle the figure that describes at best the worst pain you felt within the last 24 hours" (from 0 – no pain, to 10 the most horrible pain you could imagine) at M3

are selected in the analyzable patients population of the PHN cohort.

### 3. COLLECTED DATA

Table 3: List of procedures

	HZ COHORT		PHN COHORT		
	Inclusion	M1 ± 3 days	M3 ± 1 week	M6 ± 1 week	M9 ± 1 week
<b>Initiation activities that will be managed by the site</b>					
Aggregated demographic data	X				
Signed patient agreement	X				
Eligibility criteria	X				
Medical history	X				
Clinical Diagnosis of HZ, Procedure performed or prescribed	X				
HZ characteristics and co-morbidity	X				
HZ severity					
Healthcare resources prescribed Direct and indirect cost	X				
Patient booklet					
Report week by week HZ-related healthcare resources used between Inclusion and M1	X				
ZBPI self-administered questionnaire	X				
EQ-5D-5L Health state self-administered questionnaire	X				
<b>Follow up activities that will be managed during the phone interviews</b>					
ZBPI questionnaire		X	X	X	X
EQ-5D-5L Health State		X	X	X	X
Healthcare resources used Direct and indirect cost		X	X	X	X
Sent reminder to patient for phone interview 8-12 days before phone date		X	X	X	X
Sent the patient booklet Report week by week HZ-related healthcare resources used during the next three months			X	X	X

#### 3.1 Inclusion visit

For each patient included in the HZ cohort, physicians had to fill a paper medical questionnaire with the following information collected during patient's visit:

- Inclusion criteria
- Date of visit
- Demographics: Gender, Month and Year of birth, Occupational status - HZ characteristics:
  - o date of HZ rash onset o prodromal symptoms Yes / No (prodromal pain, hyperthermia, malaise, other – specify) o rash localization (left side, right side): head, ophthalmic zona, HZ oticus, neck, chest, arm, forearm, hand, abdomen, pelvis, thigh, leg, foot
  - o complications Yes / No:
    - cutaneous: viral dissemination, bacterial surinfection, other - specify

- ocular: lost of corneal sensitivity, keratitis, scleritis, uveitis, iridocyclitis, other - specify
- neurological: transverse myelitis, meningo-encephalitis, paralysis of cranial nerve, paralysis of peripheral nerve, syndrom of Ramsay Hunt, persistance of HZ pain, other – specify
- visceral: extension of the viral infection (bronchitis, oesophagitis, cystitis,...), viral dissemination (pneumonia, arthritis, hepatitis,...), other - specify
- ear
- other – specify
- associated comorbidities (Yes / No):
  - emotional problems, stress, depression
  - alcoholism ○ tobacco consumption ○ diabetes
  - renal insufficiency / dialysis ○ hepatic pathology
  - hepatitis C under active treatment within 12 months before HZ diagnosis
  - VIH infection with a CD4 rate < 350/ $\mu$ l or past opportunistic infection or other manifestation of AIDS at time of HZ diagnosis
  - Cancer – Solid tumor (ongoing chemotherapy or radiotherapy, or active or metastatic disease within 6 months before HZ diagnosis)
  - Malignous hemopathies (ongoing chemotherapy or radiotherapy, or active or metastatic disease within 6 months before HZ diagnosis)
  - Organ transplant within 12 months before HZ diagnosis or for 12 months or more with an ongoing anti-rejection treatment
  - Hematopoïetic cells or bone marrow transplantation before HZ diagnosis or for 12 months or more with an ongoing anti-rejection treatment
  - Active auto-immune pathology under treatment ( $\geq$  5 mg/day or more of corticoids or immunosuppressors) within 12 months before HZ diagnosis: rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, Crohn's disease, ulcerative colitis
  - Other comorbidity – specify
- Ongoing immunosuppressive treatment (Yes / No): oral or parenteral corticotherapy; chemotherapy or cytostatic treatment; monoclonal or polyclonal antibody; anti-rejection treatment – immunosuppressive treatment (cyclosporine, tacrolimus, sirolimus); other - specify

### 3.2 Patient Reported Outcomes (PRO)

#### 3.2.1 Zoster Brief Pain Inventory (ZBPI)

Developed in 2004, the ZBPI is an Herpes Zoster specific questionnaire based on the brief pain inventory (Coplan PM, 2004).

It is organized in four main chapters:

- Pain associated with HZ within the last 24 hours. If yes: place of pain, side of pain (left or right), pain at front or back

- Assessment of pain from 0 (no pain) to 10 (most horrible pain you could imagine) for:
  - o Worst pain within the last 24 hours
    - o Lowest pain within the last 24 hours
    - o Global pain within the last 24 hours
    - o Pain now
- Treatments for pain (yes/no) and relief of pain with these treatments within the last 24 hours (from 0% no change to 100% complete relief)
- Burden of pain from 0 (no burden) to 10 (complete burden) for:
  - o Global activity
  - o Mood
  - o Walking ability
  - o Usual work
    - o Relationship with others
  - o Sleep
  - o Zest of life

The questionnaire is filled by the patient during the inclusion visit on a paper form.

At 1 month, 3 months (and 6 and 9 months for the PHN cohort), the questionnaire is directly answered by the patient during the phone interview.

A postal mail or email are sent 8-12 days before the planned interview to provide self-administered questionnaires (ZBPI and EQ-5D 5L) for the interview, as well as a patient booklet that should be used by the patient to report weekly HZ-related healthcare resources used during the last three months.

### 3.2.2 EQ-5D-5L

The EuroQol Group is a network of international multidisciplinary researchers devoted to measurement of health status.

The EuroQol 5 dimensions 5 levels (EQ-5D-5L) questionnaire is a standardised measure of health status developed by the EuroQol Group, in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group, 1990).

The EQ-5D-5L comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: not at all, mild, moderate, severe, extreme or leading to incapacity.

In addition, the patient needs to score from 0 (the worst imaginable health state) to 100 (the best imaginable health state) his present health state.

The questionnaire is filled by the patient during the inclusion visit on a paper form.

At 1 month, 3 months (and 6 and 9 months for the PHN cohort), the questionnaire is directly answered by the patient during the phone interview.

### 3.3 Health care resources

#### 3.3.1 *Medical treatments for HZ and its consequences*

Treatments prescribed and taken by the patient are recorded at several time frames:

- Treatments bought by the patient before the inclusion visit (recorded by the physician on the CRF at inclusion visit)
- Treatments prescribed by the physician at the end of the inclusion visit - Treatments taken by the patient, recorded during phone interviews:
  - o Between inclusion and 1 month
  - o Between 1 month and 3 months
  - o Between 3 months and 6 months (for the PHN cohort)
  - o Between 6 months and 9 months (for the PHN cohort)

The following items are recorded, for each treatment: treatment name, dosage (mg), number of boxes, number of tablets contained in one box.

#### 3.3.2 *Sick leave for HZ and its consequences*

The prescription of sick leave is recorded at inclusion visit by the physician (yes, no), with the prescribed number of days.

Sick leaves actually made by the patient are recorded during phone interviews, with the number of days of sick leave for each sick leave, and the total number of days of sick leave on the period:

- o Between inclusion and 1 month
- o Between 1 month and 3 months
- o Between 3 months and 6 months (for the PHN cohort)
- o Between 6 months and 9 months (for the PHN cohort)

#### 3.3.3 *Medical visits after inclusion for HZ and its consequences*

At the end of inclusion visit, the physician recorded whether he sent the patient to a specialist: neurologist, dermatologist, ophthalmologist, other – specify; as well as the reason for sending: pain, cutaneous lesions, complications, other – specify.

Visits actually made by the patient are recorded during phone interviews, for visits to GPs on one hand, and for visits to specialists on the other hand (neurologist, dermatologist, ophthalmologist, other specialist – specify) with the date of visit for each of them, and the total number of visits on the period:

- Between inclusion and 1 month ○ Between 1 month and 3 months
- Between 3 months and 6 months (for the PHN cohort) ○ Between 6 months and 9 months (for the PHN cohort)

### ***3.3.4 Emergency room visits for HZ and its consequences***

Visits to emergency rooms actually done by the patient are recorded during phone interviews, with the date of the visit and the reason for the visit (pain, cutaneous lesions, complications, other – specify) for each of them, and the total number of visits to emergency rooms on the period:

- Between inclusion and 1 month ○ Between 1 month and 3 months
- Between 3 months and 6 months (for the PHN cohort) ○ Between 6 months and 9 months (for the PHN cohort)

### ***3.3.5 Hospital stays for HZ and its consequences***

At the end of inclusion visit, the physician recorded whether he sent the patient to the hospital; as well as the reason for sending: pain, cutaneous lesions, complications, other – specify.

Hospital stays actually made by the patient are recorded during phone interviews, with the number of days of the stay and the reason for the stay (pain, cutaneous lesions, complications, other – specify) for each of them, and the total number of days of stay at hospital on the period:

- Between inclusion and 1 month ○ Between 1 month and 3 months ○ Between 3 months and 6 months (for the PHN cohort) ○ Between 6 months and 9 months (for the PHN cohort)

#### 4. GENERAL STATISTICAL APPROACH

All statistical analyses will be descriptive and will provide description of the data along with 95% 2-sided CIs.

The quantitative variables are summarized using the following parameters:

- Number of non-missing data,
- Number of missing data,
- Mean,
- Standard deviation,
- Median and first & third quartiles
- Minimum,
- Maximum.

The qualitative variables are summarized using the following parameters:

- Number of non-missing data,
- Number of missing data,
- Counts and percentages

Missing data or unknown responses are not counted in the percentages, but numbers of missing data are presented in the results tables.

### 5. ANALYSIS OF PATIENT DATA

#### 5.1 Analysis variables

##### 5.1.1 Clinical Variables

All data collected by the investigator at inclusion are considered as clinical variables.

In addition, the following criteria are computed:

- Age: rounding to integer of number of months between month of birth / year of birth and month of visit date / year of visit date, divided by 12
- Age in classes: [50 – 60[, [60 – 65[, [65 - 70[, [70 – 80[, >=80 years old
- Time between start of rash and inclusion date (Days): (inclusion date – rash date) / 365.25
- Number of body sites of rash (number of sites ticked among head, ... feet)

- Total number of sites of rash (number of sites taking into account the side left or right) - Patient immunocompromised: if at least one of the following condition is met:
  - o Active auto-immune pathology under treatment ( $\geq 5$  mg/day or more of corticoids or immunosuppressors) within 12 months before HZ diagnosis
  - o VIH infection with a CD4 rate  $< 350/\mu\text{l}$  or past opportunistic infection or other manifestation of AIDS at time of HZ diagnosis
  - o Cancer – Solid tumor (ongoing chemotherapy or radiotherapy, or active or metastatic disease within 6 months before HZ diagnosis)
  - o Malignous hemopathies (ongoing chemotherapy or radiotherapy, or active or metastatic disease within 6 months before HZ diagnosis)
  - o Organ transplant within 12 months before HZ diagnosis or for 12 months or more with an ongoing anti-rejection treatment
  - o Hematopoïetic cells or bone marrow transplantation before HZ diagnosis or for 12 months or more with an ongoing anti-rejection treatment o Ongoing immunosuppressive treatment is Yes
  - o At least one treatment prescribed by investigator or declared as taken by patient at any interview amongst ATC class L04 (Immunosuppressants)

Other comorbidities recorded as free texts are standardized before analysis. Other free texts are standardized as well when necessary.

### 5.1.2 Patient reported outcomes

#### 5.1.2.1 ZBPI

Each item of the ZBPI is considered for analysis.

Items related to assessment of pain (and “worst pain” in particular) are also categorized as:

- Mild pain [0 – 3[
- Moderate pain [3 – 7[
- Severe pain [7-10]

In addition, synthetized criteria are computed when all items concerned are filled:

- Mean of assessment of pain
- Mean of burden of pain. If one item out of the 7 is missing, the mean is computed on the 6 other items.

The change of quantitative criteria from Inclusion to phone interviews at M1, M3 (M6 and M9 for PHN cohort) are assessed as well: score at phone interview – score at inclusion.

### 5.1.2.2 EQ-5D-5L

Each item of the EQ-5D-5L is considered for analysis.

A total of 3125 ( $5^5$ ) possible health states can be defined through the 5 levels of answers of the 5 dimensions of the EQ-5D-5L.

A single index value, country-specific (France for this study), is used for valorizing each health state.

Since, at time of this SAP writing, no indexes exist for the EQ-5D-5L for France, the crosswalk value set from the EQ-5D-3L computed on a study on 3691 patients with different diseases and from different countries will be used, as recommended by the EuroQol group.

The change of quantitative criteria from Inclusion to phone interviews at M1, M3 (M6 and M9 for PHN cohort) are assessed as well: value at phone interview – value at inclusion.

### 5.1.3 Health care resources

All health care resources items are considered for analysis, in addition to the costs assessments.

Medications are coded according to the Vidal dictionary. The Anatomic and Therapeutic Class (ATC) are used for categorizing treatments by:

- Anatomic class (first digit of the ATC class)
- Therapeutic class (three first digit of the ATC class)

In addition, the number of different treatments (according to the therapeutic class) is computed by time frame.

Analgesics are also classified according to their class (1, 2, 3, or local), based on names and doses of the products.

### 5.1.4 Costs assessments

The costs are evaluated by time frame:

- At inclusion
- Cumulatively up to 1 month
- Cumulatively up to 3 months
- Cumulatively from 1 to 3 months
- Cumulatively up to 6 months for PHN cohort
- Cumulatively from 3 to 6 months for PHN cohort

- Cumulatively up to 9 months for PHN cohort
- Cumulatively from 6 to 9 months for PHN cohort The type of costs evaluated are:
- Direct medical costs: hospital stays, emergency room visits, medical visits, medications - Indirect costs: patient sick leave

#### 5.1.4.1 *Direct medical costs*

##### 5.1.4.1.1 Medications

Based on the full description of the treatment name on the box,

- described by the physician at inclusion as taken by the patient before inclusion, - and given by the patient during phone interviews, the cost of the treatment by box (tax included) is retrieved thanks to the Vidal dictionary (2016).

The cost by treatment is equal to the number of boxes multiplied by the cost of the box.

The part reimbursed by the French social insurance is retrieved as well by the French Vidal dictionary.

The medication costs for one patient are the sum of all the costs of the medications taken by the patient by time frame.

##### 5.1.4.1.2 Medical visits

The costs of the medical visits are assessed according to the type of medical specialization visited (general practitioner, specialist).

Specialty	Cost (€) tax included	Part reimbursed by SS	Source
General Practitioner	23.00	70% - 1€	<a href="https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-totaux-etmoyens.php?source=2014">https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-totaux-etmoyens.php?source=2014</a>

Dermatologist	46.00	70% - 1€	<a href="https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-taux-etmoyens.phpsource">https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-taux-etmoyens.phpsource</a> - 2014
Ophthalmologist	46.00	70% - 1€	<a href="https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-taux-etmoyens.phpsource">https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-taux-etmoyens.phpsource</a> - 2014
Rheumatologist	46.00	70% - 1€	<a href="https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-taux-etmoyens.phpsource">https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-taux-etmoyens.phpsource</a> - 2014
Pain management ward	46.00	70% - 1€	<a href="https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-taux-etmoyens.phpsource">https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-taux-etmoyens.phpsource</a> - 2014
Osteopath	50.00	70% - 1€	Mean assessment
Acupuncturist	23.00	70% - 1€	<a href="https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-taux-etmoyens.phpsource">https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donneesstatistiques/professionnels-de-santeliberaux/honoraires/honoraires-taux-etmoyens.phpsource</a> - 2014

The cost for radiologists, healers, magnetizers will not be valorized.

The cost of the inclusion visit is evaluated according to the specialty of the investigator: general practitioner, dermatologist, ophthalmologist.

The cost of each medical visit recorded through phone interviews is evaluated according to the specialty visited.

The medical visit costs for one patient are the sum of all the costs of the visits made by the patient by time frame.

#### 5.1.4.1.3 Emergency room visits

No emergency room visits at all recorded in this study.

#### 5.1.4.1.4 Hospital stays

No hospital stays at all recorded in this study.

#### 5.1.4.2 *Indirect costs*

The cost of daily allowance is assessed as the overall national mean for France.

The total sum paid in France by the Social Security for daily allowances in 2012 ( $6.4 \cdot 10^9$  €) is divided by the total number of days with allowance paid in France ( $204 \cdot 10^6$  days) = 31.37 € (source: Cours des Comptes: ). The cost is acutalized to 2016, by multiplying the value by 1.0438 (evolution of cost of days of allowance from 2012 to 2016 according to DREES – PPD

██████████) = 32.74 €.

The sum of the days missed for HZ and its consequences by time frame is then multiplied to the daily allowance cost obtained.

#### 5.1.4.3 *Approaches*

Two approaches are considered for the analysis:

- The Societal approach: This approach is the most global approach, and includes the sum of all costs.
- The Payer approach: part paid by the French social security

## 5.2 Statistical methods

### 5.2.1 Disposition of physicians and patients

A flowchart will describe the physician recruitment process (contacted, refusing to participate and reasons, agreeing to participate, including patients in the HZ cohort and PHN Cohort).

Number of patients included, number and percentage of the analyzable patient population (reported on the number of patients included), will be presented globally, for patients with PHN and for patients with HZ without any PHN. Reasons for exclusion from the analyzable population are described as well (inclusion criteria not met).

### 5.2.2 Analyses

#### 5.2.2.1 Physicians' characteristics

Age and gender of active physicians having included at least one analyzable patient, will be described globally and by specialty according to the general statistical approach described in section 4.

The national statistics of age and gender published by the Department for Evaluation and statistics of the French Health Ministry for 2016 (DREES – source:

<http://www.data.drees.sante.gouv.fr/ReportFolders/reportFolders.aspx>) for France mainland will be used as descriptive reference figures for the three specialties of investigators recruited in this study (general practitioners, dermatologists, ophthalmologists).

#### 5.2.2.2 Patients' data

All analyses (see section 5.1) will be conducted globally for the HZ and for the PHN cohorts. The analysis of the HZ cohort will also be performed according to:

- gender
- classes of age: < 70 years / ≥70 years

Due to the very small sample size expected for the PHN cohort, no further subgroup of this cohort will be considered.

Patients' profiles will be produced for each of the patients of the PHN cohort.

#### 5.2.2.2.1 Clinical variables

Clinical variables (see section 5.1.1) will be analyzed in a descriptive way according to the general statistical approach described in section 4.

#### 5.2.2.2.2 Patient reported outcomes

PRO variables (see section 5.1.2) will be analyzed in a descriptive way according to the general statistical approach described in section 4, by time frame (inclusion, 1 month, 3 months, and for PHN: 6 months and 9 months).

Analysis of evolutions from inclusion will also be conducted by time frame, by use of the Wilcoxon signed rank test for quantitative criteria and by use of the Mc Nemar's test for binary criteria in the HZ cohort.

Spaghetti plots will be produced for describing the evolutions in the PHN cohort.

In addition, for the analysis of the EQ-5D-5L indexes, the reference value of the index for France for EQ5D-3L indexes (Chevalier J, 2013) is used for assessing the average loss in quality of life at inclusion and by time frame.

As a sensitivity analysis, means and 95%CI of the means of the EQ-5D-5L index will also be estimated by a generalized linear model, with Gamma distribution and log as link function.

Consistency between PRO measurements will be assessed by scatter plots crossing the individual items of the ZBPI with the individual items of the EQ-5D-5L, at baseline, at 1 month and at 3 months, for the HZ cohort.

#### 5.2.2.2.3 Health care resources

Health care resources variables (see section 5.1.3) will be analyzed in a descriptive way according to the general statistical approach described in section 4, by time frame (inclusion, 1 month, 3 months, and for PHN: 6 months and 9 months) and for the global study period.

For medications, number and percentages of patients with at least one medication by anatomical and therapeutical category (patients are counted once if many medications fall in the same category) will be presented by time frame and on the whole period.

The cumulative number of days of sick leave, the cumulative number of visits to a general practitioner, the cumulative number of visits to a specialist (globally and by specialty), the cumulative number of visits to emergency room and the cumulative number of days of hospitalization, will be presented by time frame and on the whole period.

The cumulative number of days of sick leave will also be presented by time frame and on the whole period for patients working full time or part time.

Spaghetti plots will be produced for describing the quantitative health care resources data in the PHN cohort.

### 5.2.2.3 Costs analysis

The costs assessment will be made for patients with both interviews conducted at 1 month and at 3 months. The costs assessments of the PHN cohort at 6 and 9 months will be made for patients who have also both interviews conducted at 6 and 9 months.

For both approaches (societal and payer), direct medical costs and indirect costs will be summed from inclusion up to 3 months for the global HZ cohort. For the PHN cohort, costs will be summed from inclusion up to 6 months and from inclusion up to 9 months. For the PHN cohort, costs will also be summed from inclusion up to 3 months, for comparison to the rest of the global HZ cohort.

Means and 95%CI of the means will be estimated by a generalized linear model, with Gamma distribution and log as link function.

Histograms of the costs will be produced for the HZ cohort. Values of the costs obtained in the PHN cohort will be plotted patient by patient.

## 6. DATA HANDLING CONVENTIONS

Wordings (clear text) will be standardized before analysis. The listings will be submitted to the coordinating center for validation before use in the analysis.

Missing month of dates will be considered as 06 for durations and intervals computations.

Missing days of dates will be considered as 15 for durations and intervals computations.

When the unit is year, the result will be divided by 365.25.

When the unit is month, the result will be divided by 365.25/12 (=30.4375).

### 6.1 Missing data

Missing data will not be replaced.

### 6.2 Windows for time points

Phone interviews should be conducted at 1 month +/- 3 days, at 3 months +/- 1 week (and for PHN cohort at 6 months +/- 1 week and 9 months +/- 1 week).

Automatic emails and calendar were sent to the nurses in charge of phone interviews for optimal management.

Interviews conducted > 30 days before or after the theoretical date will be considered as missing.

## **7. INTERIM ANALYSIS**

No interim analysis is planned for this study.

## **8. SOFTWARE DOCUMENTATION**

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.