Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

ECOSTIM

Budget impact analysis of discontinuing Tyrosin Kinase Inhibitors in patients with chronic myeloid leukemia achieving a complete molecular response by using probabilistic Markov approach

Protocol

Version V2.1, 22 Mars 2017

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Plateforme de recherche en pharmaco-épidémiologie
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GENERAL INFORMATION

Title	Budget impact analysis of discontinuing Tyrosin Kinase Inhibitors in patients with chronic myeloid leukemia achieving a complete molecular response by using probabilistic Markov approach (ECOSTIM)
Protocol version identifier	Version 2.1
Date of last version of protocol	22 Mars 2017
IMPACT study number	NA
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Active substance	Tyrosin Kinase Inhibitors (TKI) indicated for chronic myeloid leukemia : imatinib (ATC code L01XE01), dasatinib (ATC code L01XE06), nilotinib (ATC code L01XE08), bosutinib (ATC code L01XE14), ponatinib (ATC code L01XE24).
Medicinal product	Glivec® 100 mg (CIP code 3622475); Glivec® 400 mg (CIP code 3622498); Tasigna® 150 mg (CIP codes 4981590, 4981584); Tasigna® 200 mg (CIP codes 2168761, 2168755), Sprycel® 100 mg (CIP code 3915958); Sprycel® 140 mg (CIP code 4946174); Sprycel® 20 mg (CIP code 3776379); Sprycel® 50 mg (CIP code 3776416); Sprycel® 70 mg (CIP code 3776445); Bosulif® 100 mg (CIP code 2699352); Bosulif® 500 mg (CIP code 2699375); Iclusig® 15 mg (CIP code 3002002); Iclusig® 30 mg (CIP code 3004761); Iclusig® 45 mg (CIP code 2741982).
Product reference	NA
Procedure number	NA
Marketing authorisation holder(s)	NA
Joint PASS	No
Research question and objectives	The **research question** is to assess the budget impact of discontinuing TKI in patients with CML achieving a complete molecular response. The **main objective** is to assess the budget impact, of discontinuing TKI treatment in patients with CML in deep molecular response since at least two years, compared with current practice (treatment during entire life), between 2008 and 2015 from the healthcare system point of view, by using a probabilistic Markov model.
Country(-ies) of study	France
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2 LIST OF ABBREVIATIONS

ATC	Drug classification (*Anatomique, Thérapeutique et Chimique*)
BPE	Bordeaux PharmacoEpi, the Pharmacoepidemiology research platform of the University of Bordeaux - INSERM CIC1401
CML	Chronic myeloid leukemia
CMR	Complete Molecular Response
CNAMTS	French national health insurance fund for salaried worker (*Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés*)
CNIL	French data protection commission (*Commission Nationale de l'Informatique et des Libertés*)
DEP	Data Extraction Plan
DRG	Diagnosis-Related Groups (*or GHM for Groupes Homogènes de Malades*)
EGB	1/97th random sample of the national health insurance database (*Echantillon Généraliste de Bénéficiaires*)
HAS	*Haute Autorité de Santé*
ICD	International Classification of Diseases
INF	Interferon
TKI	Tyrosin Kinase Inhibitors
LTD	Long-Term Disease (registration for major chronic diseases with full insurance coverage of all claims related to disease)
MMR	Major Molecular Response
PMSI	National hospital discharge summary database (*Programme de Médicalisation des Systèmes d'Information*)
Ph	Philadelphia chromosome (Ph)
SAP	Statistical Analysis Plan
SAR	Statistical Analysis Report
SNIIRAM	National healthcare insurance system database (*Système National d'Information Inter-Régimes de l'Assurance Maladie*)
out of T2A	Specific hospital record of innovative and expensive products not included in DRG cost
SRG	Stay-Related Groups (*or GHS for Groupes Homogènes de Séjours*)
TFR	Treatment-Free Remission
UMRD	Undetectable Minimal Residual Disease

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4 ABSTRACT

TITLE

ECOSTIM: Budget impact analysis of discontinuing Tyrosin Kinase Inhibitors (TKI) in patients with chronic myeloid leukemia achieving a complete molecular response by using probabilistic Markov approach.

RATIONALE AND BACKGROUND

Chronic myeloid leukemia (CML) is an hematopoietic stem cell disorder in which a t(9;22) (q34;q11) reciprocal chromosomal translocation gives rise to Philadelphia chromosome (Ph) and generates the BCR-ABL1 fusion gene encoding a constitutively activated tyrosine kinase protein. Over the past decade, a broad array of drugs designed to selectively inhibit protein tyrosine kinases [i.e., tyrosine kinase inhibitors, (TKI)] have emerged as novel therapies. These treatments induce durable responses and prolong survival allowing CML patients to have a near-normal life expectancy. Two important issues must be then considered in the future: 1-the quality of life and ethical aspects of the lifetime treatment during lifetime, 2- the economic impact of treating patients during lifetime.

One of the best ways to consider these two points is to ask the question about stopping TKI in good responder patients. Previous studies showed promising results concerning patients who remained in complete molecular remission (CMR, i.e. undetectable residual disease on quantitative RT-PCR), for at least two years after imatinib was withdrawn. All molecular relapsing patients were sensitive when imatinib was re-challenged. Around 40% of these patients remain in a prolonged treatment-free remission (TFR) after treatment cessation. Considering the cost of imatinib and the number of months without treatment based on these studies, the savings in France would be 9 million €. However, since only 40 % of patients are in treatment free remission, a study, assessing the real budget impact for the healthcare system of stopping TKI in the eligible population seems necessary as no published study has ever addressed this question in France. The French National Health Insurance database (SNIIR-AM) is well suited to conduct this study since it provides exhaustive information about total costs induced by CML patients in France in both strategies (continuing or stopping TKI treatment).

RESEARCH QUESTION AND OBJECTIVES

Research question: To assess the budget impact of discontinuing TKI in patients with CML achieving a complete molecular response.

Main objective

- To assess the budget impact, of discontinuing TKI treatment in patients with CML, treated since at least 3 years and achieving deep molecular response compared with current practice (treatment during entire life), between 2008 and 2015 from the healthcare system point of view, by using a probabilistic Markov model.

STUDY DESIGN

The direct costs of the TKI treatment strategy will be estimated by the **Bordeaux PharmacoEpi (BPE) team** in a cohort of CML patients treated with TKI after extraction of data from the French nationwide claims and hospital database between 2005 and 2015. These costs will be then compared between both strategies (continuing or stopping TKI treatment).

The coordination team 1 will secondarily conduct a budget impact analysis

	by using a probabilistic Markov model elaborated within a 3 to 5 years horizon. Modelling will be performed using transition probabilities extracted from a systematic review and meta-analysis conducted according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.
POPULATION	A cohort of CML patients treated with TKI will be identified in the French nationwide claims and hospital database (SNIIRAM). **Study period between 01/01/2005 and 12/31/2015 (cf. figure) including:** • Inclusion period: 01/01/2008 to 12/31/2014; • Date of inclusion: date of the last TKI reimbursement before discontinuation which will be defined by the absence of any TKI reimbursement without the occurrence of death during at least 61 days following the 30-day coverage period of a TKI reimbursement; • History: 3-year period; • Follow-up: at least 1 year after inclusion or until death whatever occurs first. **Inclusion criteria for CML population** • Patients aged 18 years or over; • Patients with LTD registration or hospitalization for CML (primary, associated and linked ICD-10 diagnosis code, i.e. C92.1 or C921) during the study period; • Patients who discontinued their TKI treatment for the first time during the inclusion period; • Patients treated with TKI during the inclusion period with a minimum of 3 year-period of TKI regular treatment before TKI discontinuation. A 3 year-period of TKI regular treatment will be defined on the presence of at least 10 TKI reimbursements per year during the 3 years preceding TKI discontinuation. **Exclusion criteria for CML population** • Patients who proceeded to allogeneic or autogenic hematopoietic stem-cell transplant (hospitalization ICD-10 code diagnosis Z94.80) in the 3 year-period prior to or in the month following the last TKI reimbursement identified before TKI discontinuation; • Patients with HIV/AIDS (hospitalization ICD-10 code diagnosis B24) or chronic Hepatitis C or B (hospitalization ICD-10 code diagnosis B18) in the 3 year-period prior to or in the month following the last TKI reimbursement identified before TKI discontinuation; • Recent (*i.e.* in the previous year) or ongoing pregnancy at TKI discontinuation date identified by an algorithm based on codes of hospitalization diagnoses and medical procedures. Causes of TKI discontinuation will be further investigated in the cohort in order to conduct analyses only patients with a TKI discontinuation due to a complete molecular response.

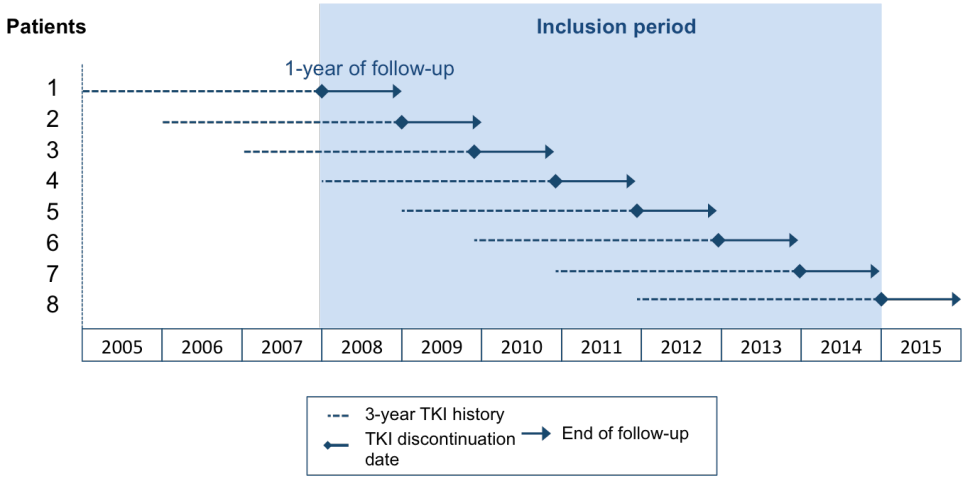

Figure 1. Study design

STUDY PERIOD

For each patient, direct medical costs will be measured and compared among different periods:

- **Period of "CML complete molecular remission" in the "TKI stop strategy"**: period from TKI discontinuation to treatment resumption or to the end of the follow-up;
- **Period of "CML molecular relapse" in the "TKI stop strategy":** period from TKI resumption to the end of the follow-up;
- **Period of "on-going TKI treatment" in the "TKI continue strategy"**: 1-year period before discontinuation including at least 10 consecutive TKI reimbursements.

VARIABLES

Baseline characteristics

- Age at TKI discontinuation;
- Comorbidities (hospitalizations and LTD).

CML characteristics

- Date of diagnosis using hospitalization date and LTD registration date;
- Specific CML treatment during the study period: TKI reimbursements or hospitalization for completion of marrow transplant.

Causes of TKI discontinuation

- Hospitalizations (with primary and associated diagnoses) during period of TKI discontinuation;
- In- or out-patient visit to haematologist at the date of discontinuation;
- Reimbursements for other drugs concomitant with discontinuation.

Vital status

- Date of death.

Healthcare resources use related

- Hospitalizations related to CML, drugs for CML and other non-drug treatments for CML, specific CML tests or imaging;
- Medical visits related to the prescription of specific CML treatment, tests or imaging, transports related to CML hospitalization or medical visits;
- Nursing acts, physiotherapy related to CML hospitalization or medical visits.

Other Healthcare resources use

- Other hospitalizations, other medical visits, other drugs, other lab tests, nursing acts, physiotherapy, transport;
- Sick leave daily allowances, pension and disability allowances.

Healthcare resources costs

From the French National Healthcare Insurance perspective based on:

- diagnosis related group for hospitalisations and claims reimbursement for outpatient healthcare resources, with direct and indirect medical and non-medical costs;
- costs reimbursed at 100% in the context of the ALD registration for CML and those partially reimbursed by the French National Healthcare insurance.

DATA SOURCES

The SNIIRAM database is the national healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims linked to the national hospital-discharge summaries database system (PMSI) and the national death registry, using a unique national pseudonymised identifier. It currently includes 98.8% of the French population, more than 66 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. The EGB is a permanent 1/97th random sample of the SNIIRAM. The SNIIRAM and EGB contain individual information on (Tuppin 2010, Moulis 2015):

- General characteristics: sex, year of birth, residence area;
- Date (month-year) of death for those concerned;
- Long-term disease (LTD) registration (International classification of disease ICD-10 codes with starting and ending date) including CML;
- Outpatient reimbursed healthcare expenditures with dates (prescription and dispensation) and codes (but not the corresponding medical indication nor result);
- Hospital-discharge summaries from PMSI: ICD10 diagnosis codes (primary, linked and associated diagnoses) for all medical, obstetric and surgery hospitalizations with the date and duration of hospitalization, medical procedures and cost coding system (DRG and SRG).

Non-hospital data are updated every month and hospital-discharged summaries are uploaded once a year, at end of Q3 for the previous year. The access to the SNIIRAM is regulated and needs approval from the "*Institut des Données de Santé*" (IDS, Institute of health Data) and the "*Commission Nationale Informatique et Libertés*" (CNIL, the French data protection commission).

STUDY SIZE

The number of new cases of CML in 2012 in France has been estimated by Institute for Public Health Surveillance (*Institut National de Veille Sanitaire*, INVS) to be around 800 patients.
A preliminary analysis was performed in the EGB database to estimate sample size of population expected in the SNIIRAM database. It was thus estimated that:

- The number of CML patients expected from 2005 and 2015 should be 19 000-25 000;
- The number of CML patients treated with TKI and with a TKI discontinuation between 2008 and 2014 should be 600-800

DATA ANALYSIS

A Statistical Analysis Plan (SAP) will be developed and will be validated by the Scientific Committee before the analysis. The statistical analysis will be performed using the SAS® software (latest current version), following a detailed statistical analysis plan.

The following analyses will be performed for the cohort:

- A flow chart depicting the number of patients and sequences of treatment available in the database satisfying the cohort criteria and follow-up duration;
- Description of baseline characteristics, comorbidities and CML diagnosis;
- Description of the duration and causes of TKI discontinuation and the resumed TKI in case of treatment resumption in the year following the discontinuation;
- Description of the healthcare resources use and costs in each study periods defined as below.

MILESTONES

EGB faisability study	Q4 2016- Q1 2017
Synopsis & Protocol	Q1 2017
Regulatory aspects and data extraction follow-up	Q2-Q4 2017
Statistical Analysis Plan (SAP)	Q3 2017
SNIIRAM data extraction	Q3-Q4 2017
Data management and statistical analysis	Q4 2017-Q1 2018
Final report	Q1 2018

5 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason

6 MILESTONES

Milestones	Planned Date
EGB faisability study	Q4 2016- Q1 2017
Synopsis & Protocol	Q1 2017
Regulatory aspects and data extraction follow-up with CNAM-TS	Q2-Q4 2017
Statistical Analysis Plan (SAP)	Q3 2017
SNIIRAM data extraction	Q3-Q4 2017
Data management and statistical analysis	Q4 2017-Q1 2018

Final report	Q1 2018

7 RATIONALE AND BACKGROUND

Chronic Myeloid Leukemia (CML) is a clonal disorder of the pluripotent hematopoietic stem cell in which a t(9;22) (q34;q11) reciprocal chromosomal translocation gives rise to Philadelphia chromosome (Ph) (Rowley, 1982) and generates the BCR-ABL1 fusion gene encoding a constitutively activated tyrosine kinase protein. CML affects about 1-2 people per 100 000 and 5000 new cases are approximately diagnosed in Europe each year.

Currently, tyrosine kinase inhibitors (TKI) such as imatinib, dasatinib and nilotinib are the “gold” standard to treat CML patients. They block BCR-ABL1 kinase activity and selectively eradicate CML cells. Tyrosine kinase inhibitors frequently induce durable responses and prolong event-free survival and progression-free survival (1). Actually, TKI treated CML patient have a near-normal life expectancy. The dramatic clinical success of imatinib and second generation TKIs has profoundly changed the outcome for CML patients. However, some of them suffer from unwanted secondary effects. Frequent side effects such as edema, cramps, and diarrhea have been reported with imatinib and for second generation TKI, such as dasatinib or nilotinib, side effects are rare but severe. Moreover, the monthly cost of imatinib is around 2 300 euros and 3900 euros for dasatinib and nilotinib. A molecular follow-up (quantitative RT-PCR) is required every three or 6 months during lifetime to detect leukemic *BCR-ABL1* transcript. The major molecular response (MMR) is defined as % *BCR-ABL1/ABL1* ≤ 0.1% on the international scale. With longer follow up, many patients treated with imatinib achieve deeper levels of response, with *BCR-ABL1 transcript* becoming undetectable in some of them (2). Undetectable *BCR-ABL1* transcript by RT-qPCR was initially designated as a complete molecular response (CMR).

If we take in account side effects of imatinib therapy during long-term treatment as well as costs considerations, being able to stop therapies has become a desirable goal (3).

Several studies were conducted to assess if CMR was maintained after TKI discontinuation in CML patients. Before 2007, molecular relapses with fast kinetics were reported in patients who stopped imatinib on their own, especially if a deep and sustained response had not been reached (4). In a previous French pilot study, imatinib was withdrawn in 12 CML patients treated and maintained in CMR for at least two years. After a median follow-up of 18 months, 50% of patients remained off-therapy without confirmed reappearance of peripheral blood *BCR-ABL1* transcripts (5). Recently, updated results showed that 50% still have an undetectable level of *BCR-ABL1* transcripts after a median follow-up of 6 years (range 4-8 years). All patients in that study had been previously treated with interferon (IFN) (6).

Those preliminary results prompted to start a multicenter study entitled ‘Stop Imatinib’ (STIM) trial. One hundred chronic phase CML patients on imatinib therapy with deep molecular response (DMR) i.e., with undetectable minimal residual disease (UMRD) for at least 2 years were prospectively included (7). Fifty-one per cent of the patients had been previously treated with IFN, and the other half were treated upfront with imatinib

only. Molecular relapse, which was arbitrarily defined as the detection of the *BCR-ABL1* transcript on 2 consecutive samples, one month apart, was a trigger for imatinib re-challenge. An interim analysis yielded promising results with a 12-months molecular relapse-free survival rate of 41% (7). A recent update of that study showed that the overall probability of maintaining CMR at 36 months was 39% (95% CI 29-48). Most patients who experienced molecular relapses did so within 6 months from imatinib cessation and remained responsive to re-treatment with imatinib as we had observed in the pilot study. Around 40% of imatinib treated CML patients with stable DMR for at least 2 years are likely to remain in a prolonged treatment-free remission (TFR) after treatment cessation (8). This rate has been confirmed by the recent Australasian TWISTER study that enrolled 40 patients with undetectable *BCR-ABL1* transcripts for at least 2 years on imatinib. At the last analysis the molecular relapse-free survival was 42.7% (9). In addition, in this study a highly sensitive patient-specific BCR-ABL1 DNA PCR showed persistence of the original CML clone in all patients with stable UMRD, even several years after imatinib withdrawal. However, the patient-specific BCR-ABL1 DNA PCR does not allow residual leukemic cells quantification (10).

Recently another multicenter French observational study (A-STIM [According to Stop Imatinib]) evaluating MMR persistence was conducted in 80 patients with CML who had stopped imatinib after prolonged CMR. In this study, the criterion of restarting treatment was less strict than in the preliminary STIM study (11). In this study, relapse was defined as the loss of MMR (i.e. %BCR-ABL1/ABL1 > 0.1%). Hence, for one third of patients a BCR-ABL1 transcript level fluctuation was observed during the molecular follow-up after imatinib stopping without relapse.

Since TKI treated CML patients have a near-normal life expectancy, two important issues must be considered in the future: i) the quality of life and ethical aspects of the lifetime treatment, ii) the budget impact, for the health care system, of treating patients during lifetime. One of the best ways to consider these two points is to ask the question about stopping TKI in good responder patients. Anyway, new results of TFR trials have to be taken into account. For instance, recently TKI withdrawal syndrome has been described. In spite of the fact that the frequency of such syndrome is difficult to know for the moment (mainly transitory i.e.; first 3 month after cessation) such a syndrome have to be taken into account (steroid prescription) (12).

No published study has assessed the efficiency of the discontinuation strategy compared with the current situation (treatment during lifetime). But as the French clinical studies (STIM 1 and 2) have shown that the treatment cessation is safe and effective, it seems obvious that it is also an efficient strategy (less costly and effective).
In this context, a budget impact analysis from the perspective of the French healthcare system will be conducted using the SNIIRAM nation-wide claims and hospital database, in order to address the expected changes in the expenditures after the adoption of this new treatment cessation strategy and provide useful information for budget holders.

8 RESEARCH QUESTION AND OBJECTIVES

The research question is to assess the budget impact of discontinuing TKI in patients with CML achieving a complete molecular response.

The main objective is to assess the budget impact, of discontinuing TKI treatment in patients with CML treated since at least 3 years and achieving deep molecular response, compared with current practice (treatment during entire life), from the healthcare system point of view between 2008 and 2015, by using a probabilistic Markov model.

9 RESEARCH METHODS

9.1 STUDY DESIGN

The direct costs of the TKI treatment strategy will be estimated by **the Bordeaux PharmacoEpi (BPE) team** in a cohort of CML patients treated with TKI after extraction of data from the French nationwide claims and hospital database between 2005 and 2015. These costs will be then compared between both strategies (continuing or stopping TKI treatment).

The coordination team 1 will secondarily conduct a budget impact analysis by using a probabilistic Markov model elaborated within a 3 to 5 years horizon. Modelling will be performed using transition probabilities extracted from a systematic review and meta-analysis conducted according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.

9.2 TREATMENTS OF INTEREST

TKI treatment for CML will be identified in the French nationwide claims and hospital database (SNIIRAM) according to their related ATC codes as follows:

- Imatinib: ATC code L01XE01;
- Dasatinib: ATC code L01XE06;
- Nilotinib: ATC code L01XE08;
- Bosutinib: ATC code L01XE14;
- Ponatinib: ATC code L01XE24.

9.3 SETTING

To assess the direct costs of the TKI strategy, data concerning CML patients treated with TKI between 01/01/2005 and 12/31/2015 will be extracted in the French nationwide claims and hospital database (SNIIRAM).

The inclusion period will be from 01/01/2008 to 12/31/2014 and the date of the last TKI reimbursement before discontinuation will be the date of inclusion in the cohort.

A TKI discontinuation will be defined by the absence of any TKI reimbursement without the occurrence of death during at least 61 days following the 30-day coverage period of a TKI reimbursement.

If a hospitalization occurs in the 30-day coverage period or in the following 5 days, the patient will be considered as being treated with TKI and the number of hospital days will be taken into account in the estimation of the TKI discontinuation.

Every patient will have a minimum of 3-year lookback period and will be followed for at least 1 year after inclusion or until death whatever occurs first.

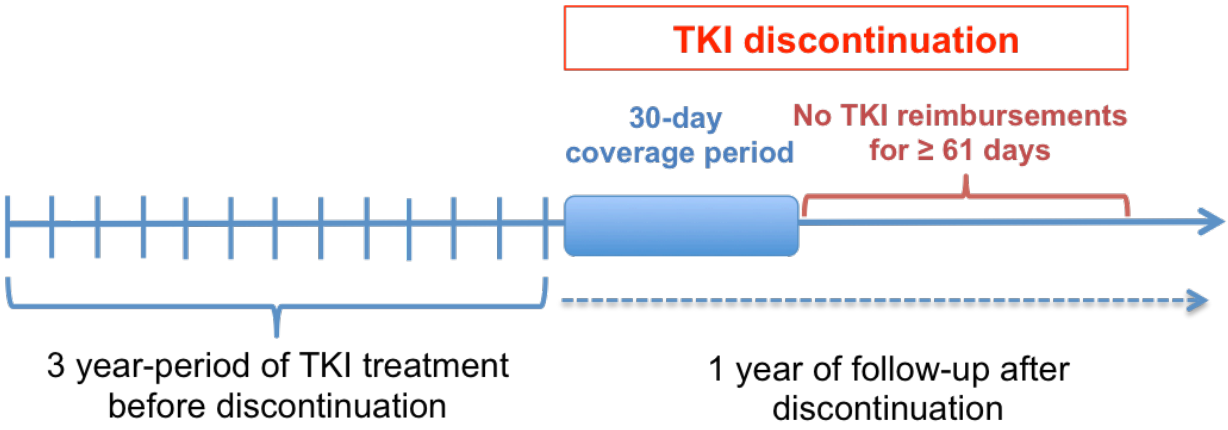

Figure 1. Definition of TKI discontinuation

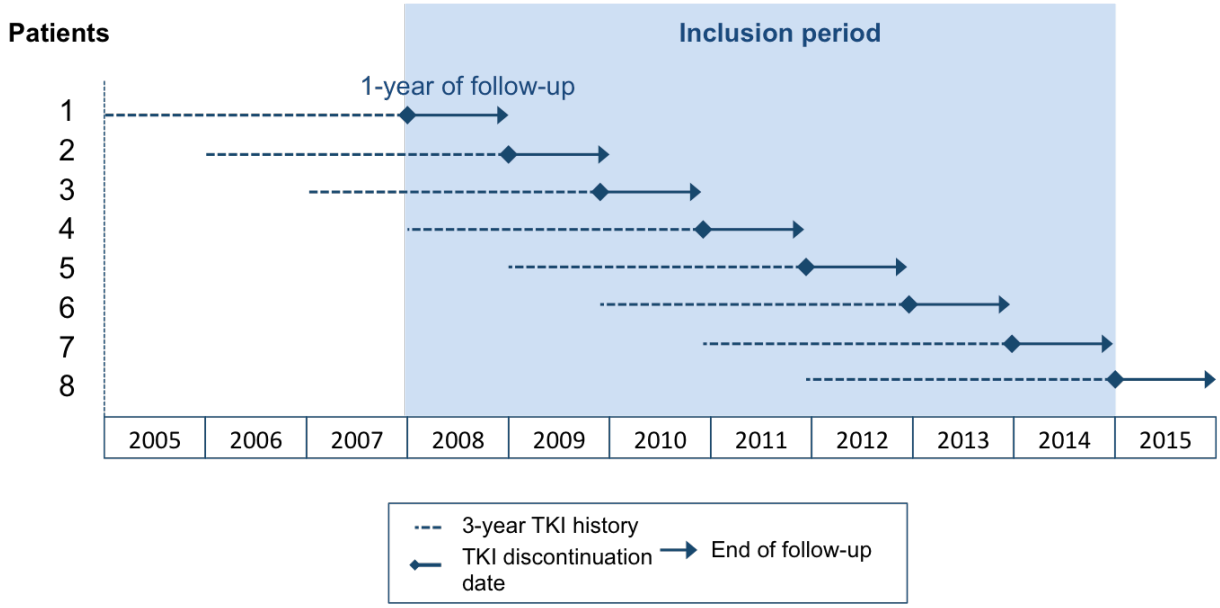

Figure 2. Description of the study design

Will be **included** in the CML cohort, all patients with the following criteria:

- Patients aged 18 years or over;
- Patients with LTD registration or hospitalization for CML (primary, associated and linked ICD-10 diagnosis code, i.e. C92.1 or C921) during the study period;
- Patients who discontinued their TKI treatment for the first time during the inclusion period;
- Patients treated with TKI during the inclusion period with a minimum of 3 year-period of TKI regular treatment before TKI discontinuation. A 3 year-period of TKI regular treatment will be defined on the presence of at least 10 TKI reimbursements per year during the 3 years preceding TKI discontinuation.

Will be **not included** in the CML cohort, all patients with the following criteria:

- Patients who proceeded to allogeneic or autogenic hematopoietic stem-cell transplant (hospitalization ICD-10 code diagnosis Z94.80) in the 3 year-period prior to or in the month following the last TKI reimbursement identified before TKI discontinuation;
- Patients with HIV/AIDS (hospitalization ICD-10 code diagnosis B24) or chronic Hepatitis C or B (hospitalization ICD-10 code diagnosis B18) in the 3 year-period prior to or in the month following the last TKI reimbursement identified before TKI discontinuation;
- Recent (i.e. in the previous year) or ongoing pregnancy at TKI discontinuation date identified by an algorithm based on codes of hospitalization diagnoses and medical procedures.

Causes of TKI discontinuation will be further investigated in this cohort of CML patients in order to conduct analyses only patients with a TKI discontinuation due to a complete molecular response.

9.4 STUDY PERIODS

For each patient, direct medical costs will be measured and compared among different periods defined as follows:

- **Period of "CML complete molecular remission" in the "TKI stop strategy"**: period from TKI discontinuation to treatment resumption or to the end of the follow-up;
- **Period of "CML molecular relapse" in the "TKI stop strategy":** period from TKI resumption to the end of the follow-up;
- **Period of "on-going TKI treatment" in the "TKI continue strategy"**: 1-year period before discontinuation including at least 10 consecutive TKI reimbursements.

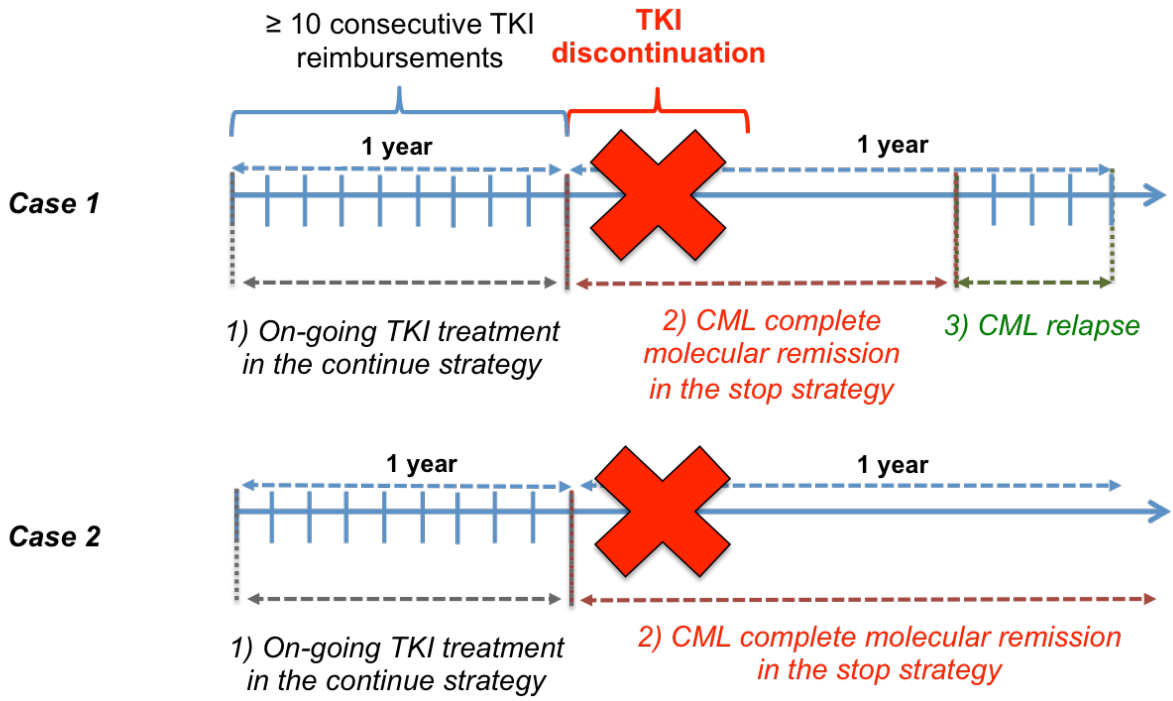

Figure 3. Study periods

9.5 VARIABLES

9.5.1 Baseline characteristics

Extracted data related to baseline characteristics will be:

- Age at TKI discontinuation;
- Gender;
- Comorbidities (hospitalizations diagnosis and LTD).

9.5.2 CML characteristics

Extracted data related to CML characteristics will be:

- Estimation of the date of diagnosis using:
  - Hospitalizations with CML diagnosis and the related date of admission during the study period;
  - LTD registration for CML and the related start and end dates during the study period.
- Specific CML treatment during the study period: TKI reimbursements or hospitalization for completion of marrow transplant.

9.5.3 Causes of TKI discontinuation

In order to investigate the causes of TKI discontinuation (complete molecular response, toxicity, etc.) the following variables will be extracted during the period of TKI discontinuation:

- Hospitalizations with primary and associated diagnoses;

- In- or out-patient visit to haematologist at the date of discontinuation;
- Reimbursements for other drugs concomitant with discontinuation.

9.5.4 Vital status

Vital status will be defined with the date of death (cause of death not available in the database).

9.5.5 Healthcare resources use

Healthcare resources use related to CML will be defined as:
- Hospitalizations related to CML;
- Drugs and other non-drug treatments for CML;
- Specific CML tests or imaging;
- Medical visits related to the prescription of specific CML treatment, tests or imaging;
- Transport related to CML hospitalization or medical visits;

Other Healthcare resources use will be classified as:
- Other hospitalizations;
- Other medical visits;
- Other drugs;
- Other lab tests;
- Physiotherapy;
- Nursing acts;
- Transport;
- Sick leave daily allowances;
- Pension and disability allowances;
- Other.

9.5.6 Healthcare resources cost

Healthcare resources cost will be estimated in euros (€) from the French National Healthcare Insurance perspective, using:
- diagnosis related group for hospitalisations and claims reimbursement for outpatient healthcare resources, with direct and indirect medical and non-medical costs;
- costs reimbursed at 100% in the context of the ALD registration for CML and those partially reimbursed by the French National Healthcare insurance.

9.6 DATA SOURCE

SNIIRAM database is the nationwide healthcare insurance system database that contains individual anonymous information on all reimbursed outpatient claims and is linked to the national hospital-discharge summaries database system (PMSI) and the national death registry, using a unique national pseudonymised identifier. It currently includes the 3 main healthcare insurance systems, and several other smaller ones, which represent more than 98.8% of the French population (66.6 million subjects) from

birth (or immigration) to death (or emigration), even if a subject changes occupations or retires. Available information concerns:

- General characteristics: sex, year of birth, date of death for those concerned, *Couverture Mutuelle Universelle-complémentaire* (CMU-c) status, residence area and, *Affections de Longue Durée* (*ALD, ie.* long-term diseases (LTD)) status with LTD main labels and associated ICD10 codes, starting and ending date of LTD;
- All non-hospital reimbursed healthcare expenditures with date and code (but not the corresponding medical indication nor result): visits and medical procedures, lab tests, drugs and medical devises;
- Hospital-discharge summaries from PMSI: ICD10 diagnosis codes (primary, linked and associated diagnosis) for all medical, obstetric and surgery hospitalizations with the date and duration of hospitalization, medical procedures, hospitalization department and cost coding system.

Non-hospital data are updated monthly with a lag of 6 months to reach about 99% of the information uploaded and hospital-discharge summaries yearly during the third quarter for the data of the previous year. Access to SNIIRAM is regulated and needs approval from institute of health data (*Institut des Données de Santé* - IDS) and the French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL).

9.7 STUDY SIZE

The number of new cases of CML in 2012 in France has been estimated by Institute for Public Health Surveillance (*Institut National de Veille Sanitaire*, INVS) to be around 800 patients.
A feasibility study was performed in the EGB database to estimate sample size of population expected in the SNIIRAM database. It was thus estimated that:

- The number of CML patients expected from 2005 and 2015 should be 19 000-25 000;
- The number of CML patients treated with TKI and with a TKI discontinuation between 2008 and 2014 should be 600-800

9.8 DATA MANAGEMENT

Database extraction criteria will be described in a Data Extraction Plan (DEP) approved prior to initiating extraction. Data extraction will be done by the CNAMTS. The BPE data manager in charge of the project will validate the population extracted by the CNAMTS using the EGB data extraction.

Data transformation, including decision rules, disease definition, exposure definition, outcomes, risk factors, healthcare resources and calculated variables will be detailed in a statistical analysis plan (SAP).

9.9 DATA ANALYSIS

9.9.1 Generalities

Statistical analysis will be performed using SAS® software (SAS Institute, latest current version, North Carolina, USA). A Statistical Analysis Plan (SAP) will be developed and will be validated before the analysis.

The BPE team will perform the following analyses on the cohort. Other specific statistical analyses could be performed with protocol amendment.

9.9.2 Population description

- A flow chart depicting the number of patients available in the database satisfying the cohort criteria;
- Description of baseline characteristics, comorbidities and CML diagnosis.

9.9.3 Treatment strategy

- Description of the duration and causes of TKI discontinuation;
- Description of the type and dose of the resumed TKI in case of treatment resumption in the year following the discontinuation;
- Description of the healthcare resources use and costs in each study periods defined as below.

9.9.4 Healthcare resources use and costs

- Description of healthcare resources use for CML and their related costs during the follow-up.

9.9.5 Probabilistic Markov approach

The coordination team 1 will secondarily conduct a budget impact analysis by using a probabilistic Markov model elaborated within a 3 to 5 years horizon. Modelling will be performed using transition probabilities extracted from a systematic review and meta-analysis conducted according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.

9.10 QUALITY CONTROL

The BPE, INSERM CIC1401, has implemented a quality management system for all its activities. CNAMTS data extraction will be validated using the expected population size estimated using the EGB. An independent double programming will be performed for main criteria and analysis, and the results compared for validation. All statistical logs are kept and can be provided. In the case of interim analysis, the database for the interim analysis is locked and kept for ulterior validation if needed. The statistical analysis report (SAR) is included in the final study report.

9.11 LIMITATIONS OF THE RESEARCH METHODS

The SNIIRAM is a national healthcare claims database linked to the national hospital discharge summaries database that covers about 99% of the French population. It provides a unique opportunity to identify all CML patients, with exhaustive information about reimbursed treatments out of hospital and use of reimbursed healthcare resources, as well as all hospitalisations. Furthermore, the SNIIRAM has the advantage of any study that use patient records from an existing database that are not impacted by the study, as most of field studies.

This is also the main limit of this claims and hospitalisation database that was built for administrative and reimbursement purposes with a lack of clinical data and biological results, including severity or stage of the disease, relapse or recurrence, or some risk factors such as smoking status, body mass index, blood pressure.

10 PROTECTION OF HUMAN SUBJECTS

This project is a database analysis with individual anonymous information for which subject informed consent is not required. Data extraction from the SNIIRAM is regulated and needs approval from Institute of Health Data (*Institut des Données de Santé* - IDS) and French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL).

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This project is a database analysis using anonymous individual information without any spontaneous reporting. Study outcomes will be reported in aggregate in the final study report, and no individual or expedited reporting is required, according to the EMA Guideline on good pharmacovigilance practices cited above (GVP IV*), as well as the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

* The latest revision of the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1) from EMA (coming into effect 16 Sept 2014) specifies: *For Non-interventional post-authorisation studies based on secondary use of data (VI.C.1.2.1.b): "The design of such studies is characterised by the secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses. For these studies, the reporting of suspected adverse reactions in the form of ICSRs is not required. Reports of adverse events/reactions should be summarised as part of any interim safety analysis and in the final study report unless the protocol provides for different reporting*".

12 PLANS FOR DISSEMINATING AND COMMUNATING STUDY RESULTS

This database analysis will be performed by the BPE, INSERM CIC1401, an academic research organisation (ARO), for which scientific communication and publication is a major component of its activities. Study methods and results will be submitted to scientific meetings and for publication in international scientific journals.

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