NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Retrospective, non-interventional study to evaluate Chronic Myeloid Leukemia treatment landscape and real-life treatment outcomes in Hungary: analysis of National Health Insurance Fund database
Protocol number	B1871064
Protocol version identifier	1.0
Date	16 Nov 2020
Active substance	bosutinib (L01XE14).
Medicinal product	bosutinib (Bosulif)
Research question and objectives	The **objectives** of this study are to describe patient demographics, clinical and disease characteristics and treatment patterns of CML in Hungary. **The primary endpoint** of this study is the overall survival of CML patients treated with tyrosine kinase inhibitors in Hungary. The OS of all enrolled patients, OS by sequence pattern and by the number of treatment lines will be analyzed. **Secondary objectives** are description of the treatment length in 1st and later lines, incidence and prevalence of CML, the patient demographics (as age, gender, comorbidities), average number of patients' comorbidities, most frequent comorbidities and patient number with comorbidities at baseline and at different treatment lines by investigated TKI, distribution of the investigated TKI therapies by treatment lines

	and the real-life treatment sequences in Hungary.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	First line treatment
2L	Second line treatment
3L	Third Line
AE	Adverse Event
BCL-ABL1	Breakpoint Cluster Region—Abelson fusion gene
CCR	Complete Clinical Response
CML	Chronic Myeloid Leukemia
DSU	Drug Safety Unit
ELN	European LeukemiaNet
EMA	European Medicine Agency
ICD -10	International Classification of Diseases – 10th revision
ICHI	International Classification of Health Interventions
IEC	Independent ethics committee
IRB	Institutional review board
MR	Molecular response
NHIF	National Health Insurance Fund
NPP	Named Patient Program
OS	Overall Survival
Ph	Philadelphia

TKI	Tyrosine Kinase Inhibitor
TTT code	The code used by NHIF to identify the medicinal product

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Study Title: Retrospective, non-interventional study to evaluate Chronic Myeloid Leukemia treatment landscape and real-life treatment outcomes in Hungary: analysis of National Health Insurance Fund database

Protocol Version and Date: Version 1.0; 16 Nov 2020

Primary Author: PPD MD, PPD Hungary

Rationale and background: Patients, with the diagnosis of chronic myeloid leukemia (CML) nowadays expect a life expectancy close to the average life expectancy, due to the availability of the targeted Bcr-Abl tyrosine kinase inhibitor (TKI) treatments. However, the majority of patients should receive continuous treatment for an indefinite period, even for the rest of their lives. Five TKIs (imatinib, nilotinib, dasatinib, bosutinib, and ponatinib) are available in Hungary in everyday clinical practice.

By the decision of the CML, treatment physicians should take into account the patient's risk classification, comorbidities and patient preferences not only by determining first-line treatment but at therapy switch. Despite the excellent results, half of the patients will eventually fail (due to intolerance or resistance) to first-line treatment, and many may require a second, third, or even additional line of therapy.

Few publications exist on real-world treatment pattern from Western Europe, but there is no such data from Hungary so far. Given the population, genetic, cultural, health condition and health care system differences on country and geographic region level, it is important to investigate real world data regionally.

Research question and objectives: The objectives of this study are to describe patient demographics, clinical and disease characteristics and treatment patterns of CML in Hungary.

The **primary endpoint** of this study is the overall survival of CML patients treated with tyrosine kinase inhibitors in Hungary. The OS of all enrolled patients, OS by sequence pattern and by the number of treatment lines will be analysed and displayed on Kaplan-Meier curve.

Secondary objectives are description of the treatment length in 1st and later lines, incidence and prevalence of CML, the patient demographics (age, gender, comorbidities), average number of patients' comorbidities, most frequent comorbidities and patient number with comorbidities at baseline and at different treatment lines by investigated TKI, distribution of the investigated TKI therapies by treatment lines and the real-life treatment sequences in Hungary.

Study design: Retrospective, non-interventional study to evaluate Chronic Myeloid Leukemia treatment landscape and real-life treatment outcomes in Hungary using the database of the National Health Insurance Fund of Hungary

Population: All patients treated with TKI based on CML diagnosis between 01 January 2011-30 June 2020**.**

Variables: The variables assessed in this study are patient demographics, clinical characteristics, comorbid conditions, chronic myeloid leukemia treatment history and TKI treatment pattern.

Data sources: Prescription claims data, outpatient and inpatient data from the database of the National Health Insurance Fund of Hungary. Hungary provides universal healthcare for its citizens, thanks to the single-payer public system, the NHIF database contains all prescription claims data of all reimbursed medicinal products, all outpatient and inpatient data from all Hungarian patients.

Study size: Approximately 1000-1200 patients' data will be analysed.

Data analysis: The mathematical algorithm required for analysis is designed and provided by RxTarget Statistical Programming and Analysis Ltd. using SQL programming language based on a preliminary study plan. The algorithm is run by experts at NHIF using primary social security number-level data from selected patients. Anonymized data is provided by NHIF in an aggregated form without any individual identification parameter based on a specific permit, with the strict consideration of data protection rules. Descriptive statistics will be applied for the variables, and no hypothesis is tested.

Milestones:

Milestone	**Planned date**
Start of data analysis	Q4 2020
End of data analysis	Q4 2020
First report	Q4 2020
Final study report	Q1 2021
Manuscript for publication	Q3 2021

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data Analysis	Q4 2020
End of data Analysis	Q4 2020
First report	Q4 2020
Final study report	Q1 2021
Manuscript for publication	Q3 2021

7. RATIONALE AND BACKGROUND

CML is a neoplastic disease whose genetic and cytogenetic changes play important roles in prognosis and treatment strategies. Philadelphia (Ph) translocation t(9;22)(q34;q11) results the BCL-ABL1 fusion gene causing a constitutively activated tyrosine kinase. The presence of the Philadelphia (Ph) chromosome or the BCL-ABL1 fusion gene is part of the diagnosis of the disease.[1] The course of the disease consists of 3 stages, the chronic, the blast phase and the accelerated phase. In the chronic phase, up to 30-40% of patients are asymptomatic and approximately 85% of patients are diagnosed in this phase.[1]

According to the international literature the incidence of chronic myeloid leukemia (CML) is 1-1.5 / 100,000 inhabitants per year. Prevalence trend to be 4 times higher than the incidence. The increase in prevalence began with the introduction of tyrosine kinase inhibitors (TKI). Based on the literature data, the average age of patients at diagnosis is 60-65 years, and CML is exceptionally rare in childhood. Slightly more men are affected by this disease than women (1.2-1.3: 1).

The primary goal of the treatment is to achieve complete cytogenetic remission and a significant molecular response. Treatment should be started immediately after diagnosis and the majority of patients should receive continuous treatment for an indefinite period, or even for the rest of their lives to control the malignant disease. TKI treatment should be withheld during pregnancy. Treatment discontinuation may be considered in patients with durable deep molecular response with the goal of achieving treatment free remission.[2]

The prognosis of chronic myeloid leukemia (CML) has changed since the introduction of imatinib in the early 2000's. Survival in CML patients changed and improved drastically with the introduction of imatinib. At the time of diagnosis, patients can expect a normal life expectancy nowdays.[5] With imatinib treatment, 8-10 years survival rates are above 80%, and the cause of death in CML patients is typically unrelated to CML, in most cases related to co-morbidities.[4,5]

The most effective treatment options are the drugs belonging to the group of tyrosine kinase inhibitors (TKIs), however, allogeneic haematopoietic stem cell transplantation is still the therapeutic option available.[1] First-, second- and third generation tyrosine kinase inhibitors are currently available. The ELN (European LeukemiaNet) 2020 guideline provides guidance for physicians to develop an appropriate treatment strategy.[2]

According to the latest guidelines (ELN 2020), beside the efficacy of the TKIs, the contraindications and typical adverse event profile, early and late toxicity profile of the available TKIs, the risk classification, patient preferences and even the existing comorbidities should be taken into account by designing the treatment plan. The results of the available first- and second-generation TKIs suggest that a more rapid and deeper molecular response can be achieved with second-generation TKIs, however, there is no significant difference in long-term survival between first-generation imatinib and second-generation TKIs (dasatinib, nilotinib, bosutinib).[2]

Close monitoring of the therapeutic response is required and made by regular monitoring BCL-ABL1 levels at specified intervals. Switching the therapy may occur in the case of relapse, resistance to the TKI or intolerable toxicity. As nowadays 5 TKIs are available, patients may receive several lines of TKI therapies. Approximately half of the patients will start 2nd line treatment after first line imatinib within 5 years of therapy.[5]

In Hungary bosutinib is accessible for patients within its EMA label since 2013 via individual reimbursement, and via regular reimbursement since 2017 in 2nd and later lines. Imatinib the first TKI for CML has been used since 2001, and generics became marketed in 2017. Nilotinib and dasatinib are reimbursed both in first- and second line of CML therapy since 2014-2015.

TKIs are the standard of care in the treatment of chronic phase. Imatinib, nilotinib and dasatinib are currently reimbursed in Hungary as first line treatment. If resistance or intolerance is developed, beside previously listed second generation TKIs even bosutinib or ponatinib are recommended by the national Finance Protocol.[3, 8] Bosutinib is not reimbursed in first line. Ponatinib is available in Named Patient Program (NPP) in later lines.

Few publications exist on real-world treatment pattern from Western Europe[6,7], but there is no such data from Hungary so far. Given the population, genetic, cultural, health condition and health care system differences on country and geographic region level, it is important to investigate real world data regionally.

8. RESEARCH QUESTION AND OBJECTIVES

The objectives of this study are to describe patient demographics, clinical and disease characteristics and treatment patterns of CML in Hungary and evaluate how these key features have changed in investigated time period.

The **primary endpoint is** overall survival of CML patients treated with tyrosine kinase inhibitors in Hungary.

- OS of all enrolled patients
- OS by sequence pattern (where patients meet the inclusion criteria and the available data allows the analysis). Sequence patterns according the actual marketing authorisation of the investigated products are listed in the Table 1.
- OS by the number of treatment lines

Secondary objectives are

- the incidence and prevalence of CML in Hungary total, and per year during the investigated period

- patient demographics (age, gender) of all enrolled CML patients
- patient comorbidities based on Charlson comorbidity index
    - average number of patients' comorbidities at baseline (start of the 1L treatment) and at different treatment lines (at the point of treatment switch regardless of the TKIs)
    - most frequent comorbidities for each investigated TKI total and by treatment lines (investigated comorbidities listed in Table 2.)
    - average number of patients' comorbidities at the start of different treatment lines (1L, 2L, 3L etc) by investigated TKIs regardless of the previous treatment
    - patient number with 0, 1, 2 or more than 2 comorbidities at the start of different treatment lines (1L, 2L, 3L etc) by investigated TKIs regardless of the previous treatment
- distribution of the investigated TKI therapies by treatment lines: 1L, 2L, 3L, 4L etc.
- description of real-life treatment sequences as listed in the Table 1.
- description of the length of each therapeutic line by investigated TKIs during real-life use and dose-intensity in each treatment line by TKIs

The use of tyrosine kinase inhibitors in the study is on label in accordance with the EMA and the Hungarian marketing authorisation.

9. RESEARCH METHODS

9.1. Study design

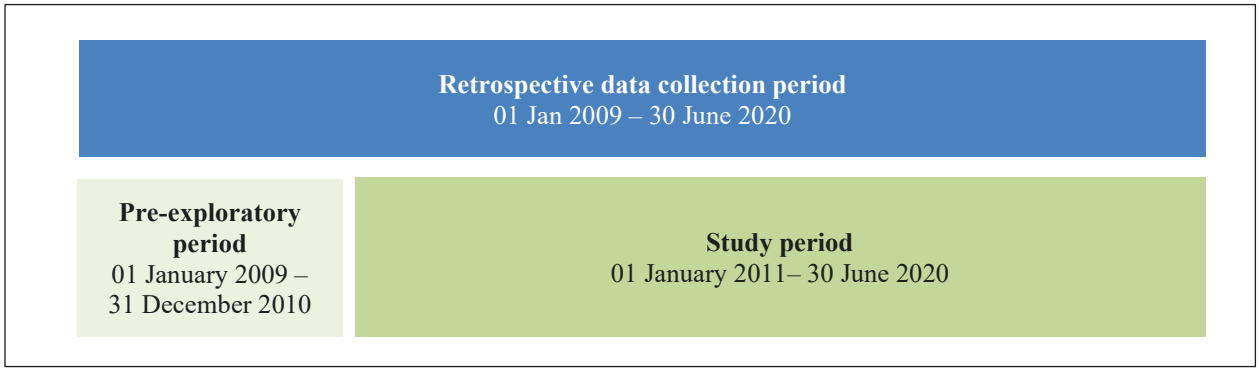
The study is a retrospective, non-interventional study to evaluate Chronic Myeloid Leukemia treatment landscape and real-life treatment outcomes in Hungary using the database of the National Health Insurance Fund of Hungary. The NHIF database is a nationwide insurance system covering close to 100% of the Hungarian population, which collects patient ID and ICD-10 code information about all in- and out-patient visits, as well as about all prescription of drugs which are reimbursed in Hungary. All data are anonymized at data extraction, and we use non-identifiable data at further analyses.

9.2. Setting

In our study, we retrospectively examine the characteristics of CML treatment, treatment patterns, and duration of treatments, focusing on tyrosine kinase inhibitor treatments by analysis on a NHIF database. From 01 January 2011, all patients treated with tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) will be included in the study

until the date of data closure (expected until 30 June 2020), this is approximately 1000-1200 patients from all Hungarian Hematology centers. Data collection starts 2 years before (01 January 2009). The analysis period, the years of 2009-2010, will be used as reference years in order to detect only the real starting therapies from 2011(Figure 1).

Figure 1. Study design



9.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Female and male patients diagnosed with chronic myeloid leukemia
2. Patients receiving tyrosine kinase inhibitor therapy under the terms of the current marketing authorization

9.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients receiving TKI for non-CML diagnoses

9.3. Variables

Variable	Role	Data source(s)	Operational definition
Age	Demographic characteristics	Medical record	Date of birth
Sex	Demographic characteristics	Medical record	Male /Female

Incidence	Disease characteristic	Medical record	Number of patients newly diagnosed with CML during the defined period
Length of treatment by lines and total	Disease characteristic	Medical record	Time from 1st CML TKI prescription to time to prescription of another CML TKI
Prevalence	Disease characteristic	Medical record	Number of all CML patients during the defined study period
Overall survival	Disease characteristics	Medical record	Time from first diagnosis of CML until death
Comorbidities at baseline	Patient characteristics	Medical record	Comorbidities coded based on the ICD-10 (listed in Table 2.) at the start of first TKI treatment for CML.
Comorbidities at different treatment lines	Patient characteristics	Medical record	Comorbidities coded based on the ICD-10 (listed in Table 2.) at switch of TKI treatment for CML
2nd line therapy	Treatment characteristic	Medical record	Use of another CML TKI therapy after 1st line
1st line therapy	Treatment characteristic	Medical record	1st prescription of any CML TKI after first CML diagnosis
Length of treatment by lines	Treatment characteristics	Medical record	Lengths of treatment analysed in each line
Number of treatment lines	Treatment pattern	Medical record	Number of therapy lines used TKI for CML

TKI distribution by therapeutic lines	Treatment pattern	Medical record	Distribution of TKI therapies among all patients in the same line of therapy

9.4. Data sources

National Health Insurance Fund's prescribing and in/outpatient database will be used for the analysis. The database is nationwide, electronic and includes all treated patients. From 01 January 2011, all patients treated with tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) will be included in the study until the date of data closure (expected until 30 June 2020). Data collection starts 2 years before the analysis period, the years of 2009-2010 will be used as reference years in order to detect only the real starting therapies from 2011.

9.5. Study size

Approximately 1000-1200 patients' data will be analysed who were treated with TKI (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) for CML between 01 January 2011 until the date of data closure (expected until 30 June 2020) will be included in the study. Data collection starts 2 years before the analysis period, the years of 2009-2010 will be used as reference years in order to detect only the real starting therapies from 2011.

9.6. Data management

The mathematical algorithm required for analysis is designed and provided by RxTarget Statistical Programming and Analysis Ltd. using SQL programming language based on a preliminary study plan. The algorithm is run by experts at NHIF using primary social security number-level data from selected patients. Anonymized data is provided by NHIF in an aggregated form without any individual identification parameter based on a specific permit, with the strict consideration of data protection rules. Descriptive statistics will be applied for the variables, and no hypothesis is tested.

National Health Insurance Fund's prescribing and in/outpatient database will be used for the analysis. The database is nationwide, electronic and includes all treated patients. The National Health Insurance Fund provides access to the database to run predefined algorithm. The database is owned by the National Health Insurance Fund.

Descriptive statistics will be applied for the variables. This includes means, median, range, percentage etc. The data of all patients treated with tyrosine kinase inhibitors for chronic myeloid leukemia in Hungary will be studied.

9.7. Data analysis

Descriptive statistics will be applied for the variables. This includes means, median, range, percentage etc. The data of all patients treated with tyrosine kinase inhibitors for chronic myeloid leukemia in Hungary will be studied.

Hungary provides universal healthcare for its citizens, thanks to the single-payer public system, the NHIF database contains all prescription claims data of all reimbursed medicinal products, all outpatient and inpatient data from all Hungarian patients.

For the analysis we use electronically stored data from the NHIF database, which display demographic data, previous treatments' and concurrent treatments' data, coded by ICD-10, ICHI and drug TTT codes using a predefined algorithm. Data are provided in anonymized form by the NHIF.

The demographics, treatment lines and treatment sequences with tyrosine kinase inhibitors will be investigated. Patients' comorbidities will also be investigated.

1. Epidemiology: age, sex, treatment lines, incidence, prevalence, mortality. For studying the epidemiology based on the NHIF database the following definitions will be used:

    - Patient population is defined as patient is coded with ICD-10 C92 between January 2009 and June 2020, has data either in outpatient or in inpatient system and/or have a TKI (imatinib, bosutinib, dasatinib, nilotinib or ponatinib) prescribed. The analysis period defined as January 2011- June 2020 (January 2009-December 2010 used as pre-exploratory period.)

    - Incidence is defined as patients newly diagnosed during a given period.

    - Point prevalence is defined as patients who were already diagnosed before the first day of the given period (up to 31 December 2008) and were still living on the first day of the given period. They are patients who are still diagnosed on the first day of the given period (cross-sectional view).

    - Period prevalence is defined as patients who were already diagnosed before the first day of the given period (up to 31 December 2008) or were newly diagnosed during a given period and were still living on the first day of the given period. They are the sum of incident and point prevalent patients (longitudinal-section view).

    - Dead patient is defined as patient who was diagnosed before the first day of the given period (up to and including 31 December 2008) or during the given period and died during the given period.

- Number of patients treated: patients who were diagnosed and also received TKI treatment at least once during the investigated period, and the TKI treatment was prescribed with C92 ICD-10. The data are also presented in line setting: the first target product (TKI) received is the 1st line treatment, the second target product (TKI) is the 2nd line treatment, and so on.

2. Length of each treatment line, overall survival (OS)

- Medication (TKIs) persistence will be analyzed in the whole investigated population and based on treatment lines. Patients will be enrolled who had first prescription of TKI during the investigated period. Data will be available both censored at death and not censored. Median and 95% CI will also be used to calculate persistence.
    - Persistence of the target product: the patient's therapy is stopped when the target product (TKI) is depleted according to our calculations
    - Persistence of total CML therapy: the patient's therapy is stopped when the patient uses none of the target product (TKI)
- Length of treatment line will be calculated and demonstrated with Kaplan-Meier curve. Progression considered as change of therapy line or death.
- Switch in treatment lines determined when the prescribed TKI for CML changed. Therapy switch can be established due to suboptimal treatment response, treatment failure or treatment intolerance. The background of the TKI switch cannot be analyzed using the NHIF's database.
- Overall survival rate: the probability that a patient is still alive for a certain period of time (% of patients). OS will be demonstrated with Kaplan-Meier curve. The method provides information on the survival of patients in a particular sequence of treatment. Patients will be enrolled who had first prescription of TKI during the investigated period.
    - Overall survival by treatment sequences, as defined in Table 1. based on the actual marketing authorization of the target TKIs

Table 1. Treatment sequence options.

	1L	2L	3L	4L	5L
1	imatinib	nilotinib	dasatinib	bosutinib	ponatinib
2				ponatinib	bosutinib
3			ponatinib	dasatinib	bosutinib
4				bosutinib	dasatinib

5			bosutinib	dasatinib	ponatinib
6				ponatinib	dasatinib
7		dasatinib	nilotinib	bosutinib	ponatinib
8				ponatinib	bosutinib
9			bosutinib	nilotinib	ponatinib
10				ponatinib	nilotinib
11			ponatinib	bosutinib	nilotinib
12				nilotinib	bosutinib
13		bosutinib	nilotinib	dasatinib	ponatinib
14				ponatinib	dasatinib
15			dasatinib	ponatinib	dasatinib
16				nilotinib	ponatinib
17	nilotinib	dasatinib	bosutinib	ponatinib	
18			ponatinib	bosutinib	
19		bosutinib	dasatinib	ponatinib	
20	dasatinib	nilotinib	bosutinib	ponatinib	
21			ponatinib	bosutinib	
22		bosutinib	nilotinib	ponatinib	
23	other				

Table 1. contains predefined treatment sequence options based on the products EMA label. However real-world sequences may differ due to the reimbursement, NPP, etc. in Hungary. Other defined as all other sequence not listed in the table and will be detailed based on the results of the analysis.

3. Comorbidities (based on Charlson comorbidity index[10]), number of comorbidities on each line:

   - We determine what comorbidities existed in patients at the time of diagnosis of CML. In addition, the distribution of CML patients without comorbidity, with 1 or 2 or more comorbidities will be analyzed.

   - Investigation of the comorbidities is based on the Charlson comorbidity index as following:

Table 2. Definitions of comorbidities

Condition	Definition upon ICD-10
Ischemic heart disease	I2000-I2590
Congestive heart failure	I50
Arrythmiac condition (including AF)	I44, I45, I47, I48, I49
Hypertonia	I10, I11, I12, I13, I15
Peripheral vascular disease	I70, I73, R02, Z958, Z959
Cerebral vascular accident	I60, I61, I62, I63, I65, I66, G450, G451, G452, G458, G459, G46, I64, G454, I670, I671, I672, I674, I675, I676, I677 I678, I679, I681, I682, I688, I69
Dementia	F01, F02, F03, F051
Pulmonary disease (lower tract)	J4
Connective tissue disorder	M32, M34, M332, M053, M058, M059, M060, M063, M069, M050, M052, M051, M353
Peptic ulcer	K25, K26, K27, K28
Liver disease	K7
Severe liver disease	K729, K766, K767, K721
Diabetes	E10-14
Diabetes complications	E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144
Paraplegia	G81 G041, G820, G821, G822
Renal disease	N03, N052, N053, N054, N055, N056, N072, N073, N074, N01, N18, N19, N25
Other cancer	C
Metastatic cancer	C77, C78, C79, C80
HIV	B20, B21, B22, B23, B24
Thromboembolic events	I26, I800-I8290
Metabolic disorders	E7800, E7810, E7820, E7830, E7840, E7850, E10-E14,

4. Dose intensity: The average doses of the investigated TKIs will be analysed by therapeutic lines regardless of the previous and following treatment.

9.8. Limitations of the research methods

Since the NHIF database only contains reimbursed prescription claims data, non-reimbursed claims (e.g. clinical trial patients or privately reimbursed treatment which is uncommon in

Hungary). The database does not contain laboratory data (e.g. neutropenia, anemia, etc.), patient parameters (e.g. body mass index), patient symptoms (e.g. fatigue) or pathological or molecular features of CML (depth of treatment response g. CCR, MR, MR4.0, MR4.5, etc.) The database does not contain information on adverse events. The database does not include data on the background of therapy switch (suboptimal treatment response, treatment failure or treatment intolerance) hence the progression free interval cannot be investigated only the length of therapy per lines.

Biases:

Selection bias: Given the retrospective data collection, the study population enrolled in this study is based on treating physician clinical decision and selection.

Information bias: Data provided by the NHIF database based on electronic health records coded, thus it has limitations, and certain information of pathological or molecular features of CML is not coded.

9.9. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

The study protocol approved by Hungarian National Institute of Pharmacy and Nutrition, and by Medical Research Council Ethical Committee

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor.

The study protocol approved by Hungarian National Institute of Pharmacy and Nutrition, and by Medical Research Council Ethical Committee.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

Hungarian DSU is informed about the study.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant (RxTarget Statistical Programming and Analysis Ltd.) is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

Peer reviewed journal publication is planned with the authorship of the investigators and statistics partner.

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14. LIST OF TABLES

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ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.