Pfizer

REAL-WORLD STUDY IN ACUTE LEUKEMIA: EPIDEMIOLOGY, TREATMENT PATTERNS AND OUTCOMES FOR B-CELL ALL AND AML IN ADULT PATIENTS FROM LATIN AMERICA – LOYAL STUDY

Statistical Analysis Plan

This is core/global SAP part of a multi-country study

X9001302

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SAP Approval and Sign-off

I confirm that I have read the contents of this SAP and its attachments. I approve the SAP in its current form.

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1. Table of Contents

2. List of Abbreviations

Abbreviation	Definition
AE	adverse event
AEM	adverse event monitoring
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
CNS	central nervous system
CR	complete remission; complete response
CRF	case report form
CRi	complete remission with incomplete hematological recovery or complete response with incomplete blood count recovery
ECOG	Eastern Cooperative Oncologic Group
EFS	event-free survival
ELN	European LeukemiaNet
EMA	European Medicines Agency
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committees
IQR	interquartile range
IRB	institutional review board
KPS	Karnofsky performance status
LOYAL	Real-world Study in Acute Leukemia: Epidemiology, Treatment Patterns and Outcomes for B-cell ALL and AML in Adult Patients From Latin America
MDR-	complete remission without minimal residual disease
NIS	non-interventional study
OS	overall survival
PPPY	per patient per year
PR	partial remission
R/R	relapsed/refractory
RFS	relapse-free survival
SAP	statistical analysis plan
SD	standard deviation
TTNT	time to next treatment
WHO	World Health Organization

3. Responsible Parties

Name	Title	Affiliation	Contact
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4. List of Amendments and Updates

Version Number	Date	Section of the SAP	Amendment or update	Reason	Major (Y/N)
1.0	18Apr 2022	Original (not applicable)			
2.0	09Dec 2022	Abbreviations, Team members, and Sections 5, 8.3.3, 8.7, 13.1.	Update	Test with 20% of the data entered in the CRF	N

5. Supporting Information

This statistical analysis plan (SAP) was developed in accordance with the study protocol Real-World Study in Acute Leukemia: Epidemiology, Treatment Patterns and Outcomes for B-Cell acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) in Adult Patients from Latin America – Loyal Study (protocol number X9001302).

This SAP was developed in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guide on Methodological Standards in Pharmacoepidemiology

6. Project Rationale and Background

To date there is scarce data on the epidemiology and treatment patterns of patients with acute leukemias in Latin America. Despite the various guidelines and recommendations for diagnosis, risk assessment, and therapy strategies most of them are not feasible in the clinical practice of a low/middle-income region. The lack of access to technologies for cytogenetic analysis and molecular profiling, besides the limit access to target therapies are important hurdles in the care of patients with AML and ALL.

There are guidelines developed by the Ministries of Health and the local hematology/oncology medical societies for ALL and AML in Brazil [1–4], Argentina [5], Colombia [6] e Chile [7–9]. However, the understanding of ALL and AML in the real-world context of developing countries is very limited. Progress in being made in the real-world setting, leading to improvements in the way the diseases are managed [10]. Therefore, this non-interventional study aims to describe the current epidemiology, treatment

patterns and health care resource use of adult patients diagnosed with B-cell ALL relapsed/refractory (R/R) and newly diagnosed (*de novo*) AML in four Latin American countries.

7. Research Questions and Objectives

The aim of this study is to describe the current epidemiology, treatment patterns, outcomes and healthcare resource use of adult patients diagnosed with B-cell ALL R/R and newly AML in four Latin American countries.

7.1. Primary Objective(s)

- To describe the clinical and demographics characteristics of newly diagnosed AML (and follow up treatment for R/R disease when available) and R/R B-cell ALL patients
- To assess treatment patterns in current practice of newly diagnosed AML and R/R B-cell ALL patients

7.2. Secondary Objective(s)

- To describe the cytogenetic and molecular profile of newly diagnosed AML and R/R B-cell ALL patients, when available
- To evaluate the risk stratification of newly diagnosed AML and R/R B-cell ALL patients
- To describe the clinically relevant events of newly diagnosed AML and R/R B-cell ALL patients
- To estimate event-free survival (EFS) of newly diagnosed AML and R/R B-cell ALL patients
- To assess patient response rate to treatment for newly diagnosed AML and R/R B-cell ALL patients
- To describe, for R/R B-cell ALL patients, treatment received when newly diagnosed for ALL (frontline B-cell ALL treatment)
- To estimate the overall survival (OS) and the 1, 3- and 5-year overall survival (OS) of newly diagnosed AML and R/R B-cell ALL patients
- To estimate relapse-free survival (RFS) for newly diagnosed AML patients
- To describe healthcare resource utilization of newly diagnosed AML and R/R B-cell ALL patients

8. Research Methods

8.1. Study Design

The current study is a retrospective multicenter non-interventional study using real-world data collected from medical records to describe the epidemiology of acute leukemias and treatment patterns among patients diagnosed with B-cell ALL R/R or AML in 4 Latin American countries: Argentina, Brazil, Chile, and Colombia. In addition, as secondary objectives, the study will also describe molecular profile, cytogenetic risk, clinical outcomes, and healthcare resource utilization of treated B-cell ALL R/R and AML patients.

All patients with newly diagnosed AML or with R/R B-cell ALL diagnosed between 01 January 2015 and 31 December 2019 will be included in the study for medical chart abstraction. Data on demographics, clinical characteristics, treatment regimens, among others will be collected. Healthcare resource utilization will be captured to understand the management pattern of both patient's population. All relevant data reported in the medical chart since diagnosis date (index date) until the study enrollment or death, whichever comes earlier, will be assessed.

8.2. Setting

8.2.1. Study Time Period

For this study, data from patients treated at public or private healthcare facilities in Argentina, Brazil, Chile, Colombia, diagnosed with R/R B-cell ALL or AML between 01 January 2015 and 31 December 2019 will be considered for the analysis.

The eligibility period of 5 years was determined to increase the overall patient representativeness, and to allow ample follow-up to assess survival outcomes.

The study will be conducted in approximately 15 sites distributed across Argentina, Brazil, Chile, and Colombia, and is expected to enroll approximately 700 patients with R/R B-cell ALL and AML in a consecutive matter. To assure the representativeness of each country, the number of sites and the total expected enrolled patients will be limited according to the country, considering the prevalence/incidence of the diseases.

Data collection will occur in a period of up to 12 months following the independent ethics committee (IEC)/ institutional review board (IRB) approval and study set up. Patients will be consecutively enrolled, considering both target population, with no set proportion of AML and R/R B-cell ALL patients to be included in the study. However, it is expected a higher proportion of AML patients in the cohort. The study period will comprise since diagnosis date (index date) until the study enrollment or death, whichever comes earlier.

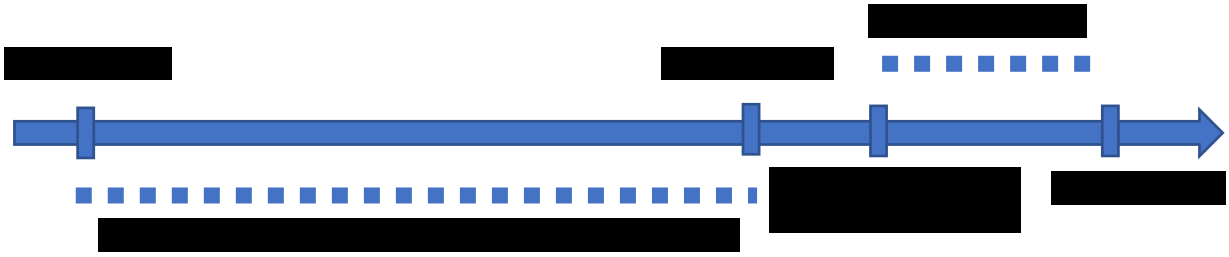

Figure 1. Study time period.

8.2.2. Index Date

Date of first diagnosis of R/R B-cell ALL or newly AML.

8.2.3. Follow-up Period and Censoring

Patients will be followed in the cohort from the index date until the end of the study period or the patient's last information available in the databases.

8.2.4. Study Population Definitions

Patients diagnosed with R/R B-cell ALL or newly AML that received at least one line of treatment for R/R B-cell ALL or newly AML within the study period.

8.2.5. Patient Selection

8.2.5.1. Inclusion Criteria

Patients will be included in the study if they fit all of the following criteria:

- Patients with ≥ 18 years old at diagnosis
- Confirmed diagnosis of R/R B-cell ALL or newly diagnosed of AML between 01 January 2015 and 31 December 2019, as documented in the medical chart and according to the physician's notes
- Patients that received at least one line of treatment for R/R B-cell ALL or newly AML within the study period; for R/R B-cell ALL patients, data on previous therapy will also be collected if available.

8.2.5.2. Exclusion Criteria

Patients will be excluded from the study if they fit at least one of the following criteria:

- Patients with no medical chart available;
- Patients with unreliable data as per investigator's opinion (e.g. excessive missing data or inconsistence data)
- Patients that have participated in any interventional clinical trial for R/R B-cell ALL or AML at any moment. Patients under any compassionate use is allowed.
- Patients with secondary AML;
- Patients with any concomitant primary malignancy;
- Patients with acute promyelocytic leukemia (APL).

8.2.5.3. Selection of Comparator Patients

Not applicable

8.2.6. Sub-Population

Not applicable

8.3. Variables

8.3.1. Exposures

Patients will be considered to have been exposed if:

- at least one line of treatment for R/R B-cell ALL or newly AML within the study period

8.3.2. Outcomes

Primary outcomes

1. Description of demographic and clinical presentation characteristics at the moment of R/R B-cell ALL or AML diagnosis
2. Treatment description considering the front-line therapy and subsequent regimen(s) required for patients with R/R B-cell ALL and AML, including any systemic chemotherapy, target therapy, hematopoietic stem cell transplantation (autologous/allogenic), intrathecal chemotherapy and palliative management.

Secondary outcomes

3. Description of subtypes of AML and B-cell ALL based on the cytogenetic and molecular abnormalities, according to the WHO classification

4. Proportion of patients of each prognostic-risk group (favorable, intermediate, adverse) among newly diagnosed AML patients, based on cytogenetic profile

5. Description of the treatment standard from diagnosis to inclusion of R/R ALL patients

6. Description of clinically relevant events presented by AML and R/R B-cell ALL patients since treatment initiation until loss of follow-up or death from any cause;

7. The EFS will be the measure of time since diagnosis until failure to achieve complete remission (CR), or disease progression after CR, or death from any cause for both AML and R/R B-cell ALL patients;

8. The OS will be the measure of median time since diagnosis until death from any cause for both AML and R/R B-cell ALL patients;

9. The OS will also assess the proportion of AML and R/R B-cell ALL patients alive after 1, 3 and 5 years, if feasible, since treatment initiation;

10. For AML patients who achieved CR, the RFS will be the measure of time since the CR attainment until relapse or death from any cause;

11. For AML patients the response to induction and consolidation therapy will assess the proportion of patients who achieve CR, complete remission with incomplete hematological recovery (CRi), complete remission without minimal residual disease (MDR-), partial remission (PR), and progressive disease

12. For R/R B-cell ALL patients the response to the rescue treatment will access the proportion of patients with CR, complete remission without MRD-, PR, and progressive disease

13. Heath care resource utilization description, considering the outpatient utilization, inpatient admissions, hospitalization length of stay, and concomitant medication prescription since diagnosis until the loss of follow-up or death from any cause.

8.3.3. Covariates

Not applicable

8.4. Data Sources

8.4.1. Databases

All information will be capture from patient´s medical chart since diagnosis until the most recent data available at study enrollment.

Screening of data in medical records will be conducted retrospectively to identify study candidates, followed by data collection from registrants in a manner consistent with each investigator's practice (with recording of data using electronic case report forms).

8.4.2. Linkage Methods

Not applicable

8.5. Study Size

As a descriptive study, sample size calculations are not applicable. The expected number of patients eligible for the study is approximately 700. An initial estimation of 15 sites across Argentina, Brazil, Chile and Colombia. The number for each disease will be estimated based on the feasibility assessment. Study size was estimated according to incidence of the diseases in Latin America and population size of each country [11]. In Latin America, the incidence varied from 0.51/100,000 to 2.0/100,000 for AML and from 0.81/100,000 to over 1.0/100,000 for ALL from 1990 until 2017 [11]. Considering all leukemia cases in 2017, global incidence trends correspond to 23.1% and 12.4% for AML and ALL, respectively. Higher trends were found in Southern Latin America, with 27.7% and 14.9% for AML and ALL, respectively. The number of sites and participants for each country are described below:

- Argentina: expected 3 sites with approximately 200 eligible patients
- Brazil: expected 4 sites with approximately 300 eligible patients
- Chile: expected 2 sites with approximately 100 eligible patients
- Colombia: expected 2 sites with approximately 100 eligible patients

8.6. Data Management

8.6.1. Statistical Software

All analyses will be conducted using SAS 9.4 or newer version or Python version 3.6.9 or newer version or a comparable statistical software package. The statistical software used will be reported at the final clinical study report.

Data management for this study will be conducted using standard IQVIA processes. The process would take into consideration any data governance imposed on the data source including any plans to handle the data outside of the institution or country of origin. IQVIA will adhere to all local and regional laws on data protection and privacy.

8.7. Data Analysis

Analyses will be descriptive in nature, as no hypothesis is being tested. Disease staging, comorbidities, demographic, clinical characteristics will be described at the date of diagnosis and/or treatment initiation for patients diagnosed with B-cell ALL R/R or AML. Treatment and clinical information will be assessed up to the most recent data available at the study enrollment. The treatments will be described in sequence according to the chronological order of administration. The duration through the number of cycles will be evaluated. Dose reduction information will also be collected. All analysis, including sub-group assessment, will be performed according to the data availability.

Continuous variables will be described as mean and standard deviation (SD), and/or as median, minimum, maximum, interquartile range (IQR, 25th and 75th percentiles). Categorical variables will be described by simple and cross contingency tabulation, with absolute frequencies and percentages. Missing values will be included in the denominators for the calculation of percentages and missing categories will be presented.

Follow-up period will be considered the time (in years) elapsed since B-cell ALL R/R or AML diagnosis until the study enrollment. It will be summarized as a continuous variable.

All time-to-event analysis will be described using Kaplan Meier methods and plots, if appropriate. The following definition and parameter analysis will be considered:

- Time to next treatment (TTNT) – considered as the time from the start date of the front-line therapy to the start date of a subsequent line of therapy. Patients without a subsequent line of therapy will be censored at study enrollment, last visit, last contact, or death, whichever comes first. It will be presented in months.
- Overall survival (OS) – considered as death from any cause from the time of initiation of diagnosis or treatment [12,13]. Patients not known to have died will be censored at study enrollment, last visit, last contact, whichever comes later. The median OS and, if feasible, the % of alive patients in 1, 3- and 5-years follow up of newly diagnosed AML and R/R B-cell ALL patients will be assessed.
- Relapse-free survival (RFS) for newly diagnosed AML patients – considered as the date of achievement of a remission until the date of relapse or death from any cause; patients not known to have relapsed or died at last follow-up are censored on the date they were last examined, study enrollment, last contact, whichever comes later. Defined only for patients achieving CR, or CRi. The RFS will be measured as the treatment end date until next treatment initiation or date of death, whichever comes first, for all AML patients who achieved Complete remission/response (CR) or Complete remission/response with incomplete hematological/count recovery (CRi) at the end of treatment.
- Event-free survival (EFS) of newly diagnosed AML and R/R B-cell ALL patients – considered as the date of initiation of treatment (or date of diagnosis, if the previous is not available) to the date of primary refractory disease, or relapse from CR, or CRi, or death from any cause; patients not known to have any of these events are censored on the date they were last examined, study enrollment, last contact, whichever comes later. The EFS will be measured as the time since AML and R/R ALL initiation of treatment (or newly AML diagnosis and newly ALL diagnosis, if treatment date is not available) until i) treatment end date (or treatment start date of the next treatment line, if the previous is not available) when treatment response was Refractory disease(5) or Relapsed from CR or CRi or recurrent disease(6) as treatment response; ii) date of death, whichever comes first.
    - Clinically relevant events:
        - Hematological toxicities
        - Hepatotoxicity
        - Gastrointestinal toxicities
        - Tumor lysis syndrome
        - Fatigue
        - Dysgeusia
        - Alopecia
        - Muscle spams
        - Infections

- Sepsis
- Secondary malignancy due to drug toxicity
- Death
- Other

Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 2.1 (V2.1) or newer version will be used as a standardised medical terminology. Medicinal product names will be codified using World Health Organisation Drug Dictionary (WHODrug), a dictionary maintained and updated by Uppsala Monitoring Centre (UMC).

The resource utilization (e.g., number of hospital admissions, hospitalization period, procedures during hospital admissions) will be presented, if possible, as mean number per patient per year (PPPY). According to the sample distribution, the data will be presented with a standard deviation (SD) or a 95% confidence interval (95% CI), which will be estimated with the most appropriate distribution, which may include Negative Binomial, Poisson or Gama distribution. The statistical distribution will be chosen with quantil-quantil plots (QQplots).

For each resource utilization, the PPPY will be calculated as the sum of all utilizations, divided by the follow up, for each patient. It will be summarized as a continuous variable.

8.7.1. Analysis Sets

All final analyses identified in this SAP will be performed by IQVIA following Pfizer Authorization of this Statistical Analysis Plan and Database Lock process.

The all subjects enrolled (ENR) set will contain all patients screened for the study, including those who provided the informed consent and the ones enrolled with an informed consent waiver (deceased patients).

The full analysis set (FAS) will contain all eligible patients.

The safety analysis set (SAF) will contain all eligible patients who receive at least one documented dose of any Pfizer product.

If there is any doubt whether a subject was treated or not with a Pfizer product, they will be assumed treated for the purposes of analysis.

8.7.2. Descriptive Analysis by Objective

1. Both clinical and demographic characteristics will be described for each newly AML and R/R B-cell ALL patients cohorts and for overall cohort (both novo AML and R/R B-cell ALL). No statistical testing will be carried out for demographic or clinical characteristics. Only descriptive data will be reported (absolute number, frequency, mean ± standard deviation, median, interquartile range, minimum or maximum).

   Demographic characteristics at diagnosis
   - Age at diagnosis
   - Gender (Female, Male)
   - Race/Ethnicity

- County of residence
- Health insurance type.

Clinical data description for newly AML patients at diagnosis

- Comorbidities at newly AML diagnosis;
  - Anxiety
  - Cardiovascular disease
  - Cerebrovascular disease
  - Chronic pulmonary disease
  - Depression
  - Diabetes
  - Dyslipidemia
  - Hypertension
  - Hepatitis B
  - Hepatitis C
  - HIV/AIDs
  - Human cytomegalovirus (HCMV)/herpes
  - Gastrointestinal disease
  - Liver disease
  - Obesity
  - Renal disease
  - Thyroid disease
  - Other
- Family history of hematological malignances;
- Prior exposure to toxic agents;
- Prior exposure to a high dose of radiation;
  - Reason for the exposure: therapeutic radiation for other cancers; accidental exposures, or other (description);
- Bleeding history;
- Tobacco consumption habits.
- Eastern Cooperative Oncologic Group (ECOG) performance status result
- Karnofsky performance status (KPS)
- Year of diagnosis

Clinical data description for R/R B-cell ALL patients at diagnosis

- Comorbidities at newly R/R B-cell ALL diagnosis
- Family history of hematological malignances;
- Prior exposure to toxic agents;
- Prior exposure to a high dose of radiation;
  - Reason for the exposure: therapeutic radiation for other cancers; accidental exposures, or other (description);
- Bleeding history;
- Tobacco consumption habits.
- ECOG performance status result
- KPS
- Year of diagnosis

2. For each treatment line, treatment pattern will be described for each newly AML and R/R B-cell ALL patients cohorts. No statistical testing will be carried out. Only descriptive data will be reported (absolute number, frequency, mean ± standard deviation, median, interquartile range, minimum or maximum) for:

Newly AML patients:

- Classification of patient for the standard AML therapy;
- Drug regimen prescribed;
- Gemtuzumab, midostaurin or venetoclax associated with the treatment;
- Regimen type;
- Treatment duration;
- Time to next treatment;
- Total number of cycles;
- Patients that withdraw and reasons for withdrawing
- Dose reduction
- CNS involvement at disease progression
- Radiotherapy
    - Duration, dose, and local of application
- Intrathecal chemotherapy
    - Drug administered intrathecally
- Stem cell transplant (SCT)
    - Laboratory exams for SCT
    - Post-transplant event
- Laboratory exams before and after treatment line

R/R B-cell ALL patients:

- Regimen type
- Drug regimen prescribed
- Treatment duration
- Time to next treatment
- Total number of cycles
- Patients that withdraw and reasons for withdrawing
- CNS involvement at disease progression
- Radiotherapy
    - Duration, dose, and local of application
- Intrathecal chemotherapy
    - Drug administered intrathecally
- Stem cell transplant (SCT)
    - Laboratory exams for SCT
    - Post-transplant event
- Laboratory exams before and after treatment line

Secondary Objective(s)

3. For each treatment line, only descriptive data (absolute number, frequency, mean ± standard deviation, median, interquartile range, minimum or maximum) will be described for cytogenetic and/or molecular testing and immunophenotyping for each newly AML and R/R B-cell ALL patients cohorts:

    newly AML and R/R AML

    - Molecular test performed
    - AML translocation result
    - Molecular profile;
    - AML WHO classification
        - AML with recurrent genetic abnormalities
        - AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1
        - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11

  - APL with PML-RARA
  - AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A
  - AML with t(6;9)(p23;q34.1);DEK-NUP214
  - AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1
  - Provisional entity: AML with BCR-ABL1
  - AML with mutated NPM1
  - AML with biallelic mutations of CEBPA
  - Provisional entity: AML with mutated RUNX1
  - AML with myelodysplasia-related changes
  - Therapy-related myeloid neoplasms
  - AML, NOS
- Immunophenotyping result

newly B-cell ALL and R/R B-cell ALL

- Molecular test performed
- Molecular profile;
- ALL cytogenetic risk classification according to WHO for B-lymphoblastic leukemia/lymphoma
  - B-lymphoblastic leukemia/lymphoma, NOS
  - B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
  - B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);BCR-ABL1
  - B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);KMT2A rearranged
  - B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1
  - B-lymphoblastic leukemia/lymphoma with hyperdiploidy
  - B-lymphoblastic leukemia/lymphoma with hypodiploidy
  - B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) IL3-IGH
  - B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);TCF3-PBX1
  - Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
  - Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
- Immunophenotyping result

4. For each cytogenetic and/or molecular testing for newly AML, the risk stratification will be described with frequencies and absolute percentages for each treatment line:

   newly AML and R/R AML

   - AML cytogenetic risk classification according to 2017 European LeukemiaNet (ELN)
     - Favorable
     - Intermediate
     - Poor/Adverse

   R/R B-cell ALL

   - ALL cytogenetic risk classification
     - Good prognosis
     - Intermediate prognosis
     - Poor prognosis
     - Undetermined prognosis

5. Data from previous treatment lines from diagnose until study inclusion will be described for newly B-cell ALL patients and R/R B-cell ALL patients. For each treatment line, no statistical testing will be carried out. Only descriptive data will be reported (absolute number, frequency, mean ± standard deviation, median, interquartile range, minimum or maximum) for:

Newly B-cell ALL patients (treatment lines from ALL diagnose until study inclusion)

- ALL cytogenetic risk classification
- Regimen type.
- Drug regimen prescribed
- Treatment duration
- Time to next treatment
- Total number of cycles
- Number of patients with dose reduction;
- Number of patients with regimen withdraw;
    - Reasons of regimen withdraw;
- Radiotherapy
    - Duration, dose, and local of application
- Intrathecal chemotherapy
    - Drug administered intrathecally
- Stem cell transplant (SCT)

6. Clinically relevant events of newly AML and R/R B-cell ALL patients will be describe by treatment line and data will be reported as absolute number, frequency, mean ± standard deviation, median, interquartile range, minimum or maximum for:

    newly AML

    - Period of start of the event from start of first-line treatment;
    - Clinical event description;
        - Hematological toxicities;
        - Gastrointestinal toxicities;
        - Hepatotoxicity.
    - Most common adverse events description

    R/R B-cell ALL

    - Period of start of the event from start of first-line treatment;
    - Clinical event description;
        - Hematological toxicities;
        - Gastrointestinal toxicities;
        - Hepatotoxicity.
    - Most common adverse events description

7. To each newly AML and R/R B-cell ALL patients, the EFS will measure time since the date of initiation of treatment (or newly AML diagnosis and newly ALL diagnosis, if the previous is not available) until i) treatment end date (or treatment start date of the next treatment line, if the previous is not available) when treatment response was Refractory disease(5) or Relapsed from CR or CRi or recurrent disease(6); i) date of death, whichever comes first. This time-to-event analysis will be described summarized in tables and using Kaplan Meier methods and plot, if appropriate. Patients not known to have any of these events are censored on the date they were last examined:

    newly AML

    - Descriptive (median and CI(95%) estimations of Kaplan-Meier) of EFS;
    - Time categorized count and percentages.

    R/R B-cell ALL

    - Descriptive (median and CI(95%) estimations of Kaplan-Meier) of time between treatment initiation and R/R event in months;

- Time categorized count and percentages.

8. The OS will be measure for both newly AML and R/R B-cell ALL patients as median time since newly diagnosis or treatment initiation until death from any cause. This time-to-event analysis will be described using a Kaplan Meier plot, if appropriate

   newly AML
   - Descriptive (median and CI(95%) estimations of Kaplan-Meier) of time between date of diagnosis or treatment initiation and R/R event in months;
   - Time categorized count and percentages.

   This analysis will also be described for fit and non-fit newly AML patients.

   R/R B-cell ALL
   - Descriptive (median and CI(95%) estimations of Kaplan-Meier) of OS;
   - Time categorized count and percentages.

9. The median OS and the percentage (and 95% confidence intervals) of alive patients in 1, 3- and 5-years, if feasible, follow up of newly diagnosed or treatment initiation AML and R/R B-cell ALL patients will be assessed. The OS will be defined as median time since newly diagnosis or treatment initiation until death from any cause. This time-to-event analysis will be described using a Kaplan Meier plot, if appropriate.

   newly AML
   - Descriptive (median and CI(95%) estimations of Kaplan-Meier) of time between treatment initiation and death in months;
   - Time categorized count and percentages.

   This analysis will also be described for fit and non-fit newly AML patients

   R/R B-cell ALL
   - Descriptive (median and CI(95%) estimations of Kaplan-Meier) of time between treatment initiation and death in months;
   - Time categorized count and percentages.

10. For all AML patients who achieved Complete remission/response (CR) or Complete remission/response with incomplete hematological/count recovery (CRi) at the end of treatment, the RFS analysis will consider the treatment end date until date of next treatment initiation or date of death, whichever comes first. This time-to-event analysis will be described using a Kaplan Meier plot, if appropriate.

    newly AML
    - Descriptive (median and CI(95%) estimations of Kaplan-Meier) of RFS
    - Time categorized count and percentages.

11. For newly AML patients, each treatment response (induction and consolidation therapy) will assess the proportion of patients who achieve complete remission (CR), complete remission with incomplete haematological recovery (CRi), complete remission without minimal residual disease (MDR-), partial remission (PR), and progressive disease. No statistical testing will be carried out. Only descriptive data will be reported (absolute number, frequency, mean ± standard deviation, median, interquartile range, minimum or maximum) for.

Newly AML patients:

- Treatment response
  - CR,
  - CRi,
  - partial remission/response,
  - progressive disease,
  - refractory disease,
  - relapsed from CR or CRi or recurrent disease,
  - other
- Minimal residual disease (MRD) evaluation for patients that achieved CR or CRi and the diagnose method for MRD evaluation
- Patient status description

12. For R/R B-cell ALL patients, each treatment response (to rescue treatment) will access the proportion of patients with complete remission (CR), complete remission without minimal residual disease (MRD-), partial remission (PR), and progressive disease. No statistical testing will be carried out. Only descriptive data will be reported (absolute number, frequency, mean ± standard deviation, median, interquartile range, minimum or maximum) for.

R/R B-cell ALL patients:

- Treatment response
  - CR,
  - CRi,
  - partial remission/response,
  - progressive disease,
  - refractory disease,
  - relapsed from CR or CRi or recurrent disease,
  - other
- minimal residual disease (MRD) evaluation for patients that achieved CR or CRi and the diagnose method for MRD evaluation
- Patient status description

13. Heath care resource utilization description, considering the outpatient utilization, inpatient admissions, hospitalization length of stay, and concomitant medication prescription since diagnosis until the loss of follow-up or death from any cause. No statistical testing will be carried out. Only descriptive data will be reported (absolute number, frequency, mean ± standard deviation, median, interquartile range, minimum or maximum) for.

Newly AML patients:

- Number of hospitalizations;
- Reason for hospitalizations;
- Hospitalizations description
  - ICU period (days)
  - Procedures
  - Surgery
  - Blood transfusion
- Treatment time (descriptive and time categorized count).
- Concomitant medication description

R/R B-cell ALL patients

- Number of hospitalizations;
- Hospitalizations description
  - ICU period (days)
  - Procedures
  - Surgery
  - Blood transfusion
- Treatment time (descriptive and time categorized count).
- Concomitant medication description

8.7.3. Multivariate Analysis by Objective

Not applicable

8.7.4. Adjustment for Confounding

If possible, the following adjustment for confounding will be performed according to the data availability:

- age
- country
- cytogenetic risk
- ECOG performance status

8.7.5. Effect Modification

Not applicable

8.7.6. Sub-group Analysis

Sub-group analyses will be conducted as stated in the analysis sections. It should be noted that the study was not designed to detect treatment differences within sub-groups. The following sub-groups will be assessed according to the data availability and described within the analysis sections, as appropriate:

Upon availability of data, primary objectives (clinical and demographics characteristics, and treatment patterns) and survival secondary objectives (EFS, OS, RFS) analysis will be stratified by the:

- ECOG
  - 0-1
  - 2-5
- cytogenetic risk

- newly AML: favourable, intermediate and poor/adverse
- R/R B-cell ALL: good prognosis, intermediate prognosis, poor prognosis and undetermined prognosis

- country
  - Argentina,
  - Brazil
  - Chile
  - Colombia
- age range
  - ≤ 39 years old at diagnosis
  - 40 – 64 years old at diagnosis
  - ≥ 65 years old at diagnosis

8.7.7. Missing Data

Missing values will be included in the denominators for the calculation of percentages and missing categories will be presented. In general, missing data will not be imputed, and the data will be analyzed as they are recorded in the study CRFs. However, if more than 10% of data is missing for one or more key variables, the impact of missing data on the analysis will be discussed, and the pattern of missing data may be explored. If there is evidence of bias in the missing data, and variables that are considered good predictors of the missing data are available, the multiple imputation method at the study level may be used to replace missing values as secondary exploratory analyses. If the multiple imputation method is used, a sensitivity analysis will be carried out comparing results from the complete case analysis (where records with missing data will be dropped) and the full set analysis (with imputed data). Another potential strategy is a mixed-effects model repeated measures analysis. This approach helps to conserve patient data in the event of missing observations. It is also potentially advantageous in registry studies with often irregularly spaced clinic visits and observations.

8.7.8. Pooling and Meta-Analysis

Not applicable

8.8. Limitations of the Statistical Analysis

Data collected from source documentation and entered into the electronic CRF will be described. No imputation for missing data will be conducted. The loss to follow-up, including patients early discontinuing the treatment, the transference of treatment institution, or patients for whom the death was not documented in their chart, consists of an intrinsic limitation of the retrospective study design.

8.9. Quality Control

IQVIA Quality Management System (QMS)

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of IQVIA Quality Management System (QMS) and in accordance with the global procedure RWI_OP_BIOS0006RW: Biostatistics for Non-Interventional Studies and Low Intervention Clinical Trials, and RWI_WI_BIOS0021: Biostatistics Quality Control for Analysis Datasets and Statistical Output, which include quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions and study report.

9. Protection of Human Subjects Related to the Analysis

This research presents no more than minimal risk of harm to patients and involves no physical procedures with patients, therefore, a waiver of informed consent will be requested as only retrospective collection of anonymized, non-personally identifiable data will be performed. Alternatively, patients will be informed accordingly, and will be asked to give their consent on data handling procedures in accordance with national regulations in place in each of the countries included in the study.

All data will be extracted from patient´s medical chart and entered into an electronic CRF specifically designed to capture relevant information in accordance with the study outcomes. Prior to the enrolment of any patient, the study must be evaluated by the local independent ethics committees (IEC) and/or institutional review board (IRB) and a formal approval must be provided.

10. Management and Reporting of Adverse Events/ Adverse Reactions

Pursuant to the European Medicines Agency (EMA) requirements for reporting of adverse events for secondary data (GVP module VI, VI.C.1.2.1.2), adverse event reporting will not be conducted as part of this study given the study objectives will be met through the use of secondary data.

This study requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the Case report form (CRF) and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for “Illness”, “Study Drug”, and “Drug Name” may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *“YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)”*.

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a “Confirmation of Training Certificate” (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

11. 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 investigator 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.

This study aims to achieve quality results to be published in abstracts/posters at national and international scientific congresses and/or peer reviewed journals. The authors of all publications resulting from this study will be determined in accordance with the requirements of the International Committee of Medical Journal Editors (ICMJE), which states:

- Authorship should be based on: (1) substantial contributions to the design and design of the study, data collection, or analysis and interpretation of data, (2) critical writing or review of its content, (3) final approval of the version to be (4) agree to be responsible for all aspects of the work to ensure that issues related to the accuracy or completeness of any part of the work are properly investigated and resolved. Authors must comply with conditions 1, 2, 3 and 4. All authors should be identified in accordance with ICMJE criterion 1 with the expectation that they will provide input on the publication to meet criteria 2-4. Criteria 1 stipulates that a substantial contribution prior to the publication is required."

- When the research is conducted in multiple centers, the group should identify individuals who accept direct responsibility for the manuscript. These individuals must fully comply with the authorship criteria defined above. A limit of seven authors from the seven centers with the largest number of participants will be invited as authors.

- Obtaining funding, data collection or general supervision of the research group does not justify the authorship;

- All persons designated as authors must be qualified for authorship, and all qualified persons should be listed;

- Each author must have reasonably participated in the research in order to assume public responsibility for appropriate parts of the content.

12. References

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13. Annexes

13.1. TLF

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