Multicenter, open-label, Phase Ib/II trial to evaluate safety and efficacy for the combination of bosutinib plus atezolizumab in newly diagnosed chronic myeloid leukemia patients

Protocol Number:	**ZEROLMC-01**
Study Phase:	**Ib/II**
Products Name:	**Bosutinib (Bosulib®, Pfizer) and Atezolizumab (Tecentriq®, Roche Registration GMBH)**
EudraCT Number:	**2020-000166-41**
Sponsor:	**Fundación ZeroLMC (Fundación Española para la curación de la Leucemia Mieloide Crónica)** **Plaza San Francisco, S/N, portal 13, planta 1, puerta 5** **50006 Zaragoza**
Protocol Issue Date:	**May 05th, 2021**
Version Number:	**2.0**

PROTOCOL REVISION HISTORY

Protocol Version	AMENDMENT RATIONALE	Changes To The Protocol
Version 1.1 (13/11/2020)	Responses to clarifications requested by the Ethics Committee	Section 11.6.2.12 Systemic Immune activation. Management of grade 4 adverse reactions have been changed to: Permanently discontinue atezolizumab and contact the Sponsor. Consider referring to an immunologist for evaluation Consider treatment with methylprednisolone, or equivalent, or the best way of treatment according to the physician's judgement
Version 1.2 (02/12/2020)	Responses to clarifications requested by AEMPS	• Section 9.3.1 Group 1: The first 10 patients and Study Design (Protocol Synopsis). "At the investigator discretion is deleted from the definition to eliminate subjective criteria to DLT. definition. It is specified that DLTs will be graded according to the NCI CTCAE. • High-efficacy birth control methods of inclusion criteria 7.c. are adjusted according to CTFG Recommendations. • Test pregnancy each month during the study is added into the section 12.7, section 13.14, and tables 14, 15, 16 and 17. • Section 15.5 Sample Size Calculation and Statistical Analysis within the protocol synopsis are updated to make clear that it is expected that 15% of the 36 patients that will be included will not enter in bosutinib and atezolizumab combination treatment and, therefore, approximately 30 subjects will be evaluated for the combination. References to previous studies have been added. • The sentence "Women of childbearing potential must have a negative pregnancy test documented prior enrollment." Has been added to the inclusion criteria number 7 within the protocol summary. • Definition of women of childbearing potential has been rewritten in section 10.2 Inclusion criteria, to match CTFG recommendations. Reference has been added.
Version 2.0 (05/May/2021)	Recently the AEMPS have granted the authorization of commercialization of the 400 mg tablets in Spain, and could be used for the purposes of this trial	• Section 11.1 study treatments: Bosutinib (Bosulif® 400 mg film-coated tablets, Pfizer S.L.U.) is added to the study drugs.

Protocol Version	AMENDMENT RATIONALE	Changes To The Protocol
	reducing the number of tablets that the patients will have to take each day. Correction of minor typographic mistakes	• Section 11.2.1 Bosutinib Treatment**:** The possibility that only 1 tablet of 400 mg could be prescribed to the patients is included. • Section 11.3.1 Bosutinib treatment: Tablets containing 400 mg of Bosutinib as active ingredient are included in this section • Table 14, ○ Header. 860 mg of Atezolizumab is corrected to the right concentration, 840 mg. ○ Visit 2, 4 and 6: eliminate the pregnancy test from these visits. • Tables 15 and 17: assessments for 4th Phase is corrected to assessments for 3rd Therapy • Section 12.17 Pregnancy Test: Include the possibility to conduct the pregnancy test during visit 1, before drug administration.

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1 SIGNATURE PAGES

1.1 Sponsor Signature Page

Fundación Zero LMC has approved this protocol and assures that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

Name	**Signature**	**Date (dd-mmm-yyyy)**
Name	**Signature**	**Date (dd-mmm-yyyy)**
Name	**Signature**	**Date (dd-mmm-yyyy)**

1.2 Investigator Signature

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will follow this protocol as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the designated time. I will provide copies of the protocol and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study drug and the study. I understand that the study may be terminated or enrollment suspended at any time by the sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this trial in compliance with the protocol, GCP and the applicable regulatory requirement(s).

Investigator's Name	**Investigator's Signature**	**Date (dd-mmm-yyyy)**

2 CONTACT INFORMATION

Sponsor	Fundación Española para la Curación de la Leucemia Mieloide Crónica (Fundación Zero LMC) Plaza San Francisco, S/N, portal 13, planta 1, puerta 5 50006 Zaragoza Spain Telephone: +34 976 306 420
Sponsor Medical Monitor:	Ignacio Galicia, Clinical Pharmacologist, MD Head of the Clinical Investigation Department Fundación Teófilo Hernando Telephone: +34 - 636 849 505 E-mail: ignacio.galicia@ifth.es
Sponsor Monitor:	Aurelio Morales Guerrero CRA Fundación Teófilo Hernando Telephone: +34 – 911 923 700 E-mail: aurelio.morales@ifth.es
Coordinating Investigator:	Dr J Valentín García Gutiérrez Scientific Expert Servicio Hematología y Hemoterapia Hospital Ramón y Cajal E-mail: jvalentingg@gmail.com
Sponsor Pharmacovigilance and Risk Management	Clinical Investigation Department Fundación Teófilo Hernando Telephone : +34 – 911 923 700 E-mail: farmacovigilancia@ifth.es

3 ABBREVIATIONS

Abbreviation	Definition
2GTKIs	2nd Generation Tyrosine Kinase Inhibitors
ABL	Abelson leukemia oncogene
AC	Accelerated Phase
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/SGPT
ANC	Absolute Neutrophil Count
AP	Accelerated Phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
AUC	Area Under the Curve
BAL	Bronchoalveolar lavage
BC	Blast Crisis
BCR	Break point Cluster Region
BCR-ABL	BCR-ABL oncoprotein product of BCR-ABL fusion gene
BM	Bone Marrow
BP	Blast Phase
BUN	Blood Urea Nitrogen
CBC	Complete blood count
CCAA	Comunidades Autónomas (Autonomous Communities)
CCyR	Complete Cytogenetic Response
CEIm	Ethics committees for investigation with medicinal products.
CHF	Congestive Heart Failure
CHR	Complete Hematologic Response
CIB	Clinical Investigator's Brochure
CML	Chronic Myeloid Leukemia
CMR	Complete Molecular Response
CP	Chronic Phase
CP-CLM	Chronic phase Chronic Myeloid Leukemia
CRA	Clinical Research Associate
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or paper
CRO	Clinical Research Organisation
CRP	C-Reactive Protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Clinical Trial Assistant
CTCAE	NCI Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation

Abbreviation	Definition
CYP3A4	Cytochrome 3A4
CyR	Cytogenetic Response
DLT	Dose-Limiting Toxicity
EC	European Commission
eCFR	Electronic Case Report Form
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/record Form
EDC	Electronic Data Capture
ELN	European Leukemia Net
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ESR	Expedited Safety Report
FAS	Full Analysis Set
FDA	Food and Drug Administration (USA)
FISH	Fluorescent In-Situ Hybridization
FPFV	First Patient First Visit
FTH	Fundación Teófilo Hernando
GCP	Good Clinical Practice
GELMC	Grupo Español de Leucemia Mieloide Crónica
GGT	Gamma-glutamil transpeptidase
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IL-2	Interleukin-2
IM	Imatinib
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IS	International Scale
IUD	IntraUterine Device
IUS	IntraUterine System
IV	Intravenous
IVIG	Intravenous Immunoglobulin
Kg	Kilogram
LFT	Liver Function Test
LN	Lymph Node
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction

Abbreviation	Definition
MCyR	Major Cytogenetic Response
MCyR	Minor Cytogenetic Response
MDSC	Myeloid Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MMR	Major Molecular Response
MR	Molecular Response
MR4	Molecular Response 4.0 log reduction from baseline
MR4.5	Molecular Response 4.5 log reduction from baseline
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
n-TEAE	No Treatment Emerged Adverse Event
NYHA	New York Heart Association
OD	Once Daily
OS	Overall Survival
PCR	Polymerase Chain Reaction
PCyR	Partial Cytogenetic Response
PD-L1	Programmed Death-ligand 1
PFS	Progression Free Survival
Ph+	Philadelphia chromosome
PHI	Protected Health Information
PPS	Per-Protocol Set
Pts	Patients
Q2WK	Every 2 weeks
QD	Once a Day
QT	QT interval; a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTcF	QT interval corrected (Fridericia)
REB	Research Ethics Board
REec	Registro Español de Estudios Clínicos
RP3D	Recommended Phase III Dose
RR	Relative Risk
RT-qPCR	Real Time-Quantitative Reverse Transcription PCR
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBil	Total Bilirubin
TEAE	Treatment Emerged Adverse Event

Abbreviation	Definition
TFR	Treatment-Free Remission
TFS	Treatment-Free Survival
TKI	Tyrosine Kinase Inhibitor
Treg	Regulatory T cells
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
VAD	Ventricular Assist Device
VOE	Vascular Occlusive Event
WBC	White Blood Cell
WHO	World Health Organization

4 DEFINITION OF TERMS

Assessment	A procedure used to generate data required by the study.
Accelerated Phase (AP)	• ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate; • ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate; • ≥ 20% basophils in the peripheral blood; • Thrombocytopenia (<100 x 10^9/L) that is unrelated to therapy.
Blast Crisis (BC)	≥ 30% blasts in peripheral blood or bone marrow aspirate Appearance of extra medullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).
Complete Hematologic Response (CHR)	• Complete normalization of peripheral blood counts with leukocyte count <10 x 10^9/L • Platelet count <450 x 10^9/L • No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood • No signs and symptoms of disease with disappearance of palpable splenomegaly
Complete Molecular Response (CMR)	Undetectable BCR-ABL levels with high sample sensitivity (10^{-5} or greater) for a minimum of 2 years.
Cytogenetic Response (CyR)	• Complete (CCyR): 0% Ph+ metaphases. • Partial (PCyR): > 0 to 35% Ph+ metaphases. • Minor (mCyR): >35 to 65% Ph+ metaphases. • Minimal: >65 to 95% Ph+ metaphases. • None: > 95 to 100% Ph+ metaphases.
Cycle of treatment	28 days of treatment
Disease Progression	The following events are considered disease progression: • AP. • BC. • CML-related death.
Enrollment	It is the time until all patients are included in the study, i.e. all patients received at least one dose of study medication. Previously they must have signed an informed consent (i.e., prior to starting any of the procedures described in the protocol).
Full Analysis Set (FAS)	The full analysis set (FAS) comprises all patients who complete the treatment with bosutinib in combination with atezolizumab for 12 cycles successfully.
Medicinal product for Human Use or Investigational Drug	Any substance or combination of substances presented as having properties for treating or preventing disease in human beings or which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis (*Royal Decree 1090/2015, of 4 December).*
Loss of Complete Hematologic Response	Loss of CHR is defined as the appearance of any of the following, confirmed by a second determination ≥ 4 weeks later (unless associated with progression to AP/BC or CML-related death): • WBC count that rises to > 20.0 x 10^9/L; • Platelet count that rises to ≥ 600 x 10^9/L;

	• Progressing hepatosplenomegaly to a size ≥ 5 cm below the left intercostal margin; • Appearance of ≥ 5% myelocytes + metamyelocytes in the peripheral blood; • Appearance of blasts or promyelocytes in the peripheral blood.
Molecular Response (MR)	• MMR – BCR-ABL ≤ 0.1% (IS). • MR4 – BCR-ABL ≤ 0.01% (IS). • MR4.5 ≤ 0.0032% (IS). • UNDETECTABLE.
Overall Survival (OS)	OS is calculated from the first day of therapy to the date of death. Surviving patients will be censored at the time of the last follow-up.
Subject Number	A unique identifying number assigned to each patient who enrolls (i.e. signs the IC) in the study.
Per-Protocol Set (PPS)	A subset of the full analysis set (FAS) who is compliant with the clinical study protocol (i.e. Composed by subjects that have not incurred in major protocol deviations that could jeopardize the validity of the data and the study outcomes).
Premature Patient Withdrawal	When a subject exits from the study prior to the planned completion of all study treatment administration and/or assessments or procedures. From this time, all study treatment administration is discontinued and no further assessments or procedures will be done, other than the monitoring for progression and/or survival.
Progression Free Survival (PFS)	Progression free survival (PFS) is defined as the time from the date of first treatment administration until the time of disease progression. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who do not progress nor die will be censored on the date of their last hematological assessment.
Safety Set (SS)	Composed by all subjects who received at least one dose of study medication.
Study Treatment	Includes any drug or combination of drugs in any study arm administered to the subject as part of the required study procedures.
Trial Subject	An individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.

5 PROTOCOL SYNOPSIS

Sponsor	Fundación Española para la Curación de la Leucemia Mieloide Crónica (Fundación Zero LMC) Plaza San Francisco, S/N, portal 13, planta 1, puerta 5 50006 Zaragoza Spain Telephone: +34 976 306 420
Study Treatment	Bosutinib and Atezolizumab
Study Title	Multicenter, Open-Label, Phase Ib/II Clinical Trial to Evaluate Safety and Efficacy for the Combination of Bosutinib plus Atezolizumab in newly diagnosed Chronic Myeloid Leukemia Patients
Phase	Phase Ib/II
Eligible Population	Naïve patients with chronic-phase Chronic Myeloid Leukemia (CP-CML)
Summary and Study Rationale	Since the introduction of imatinib and subsequent second-generation tyrosine kinase inhibitors (2GTKIs), the prognosis of chronic-phase Chronic Myeloid Leukemia (CP-CML) has improved greatly. Initially considered a lethal disease with a median estimated overall survival (OS) of 3.2 years, CP-CML is now regarded as a chronic disease with a life expectancy similar to that of the healthy population. However, Chronic Myeloid Leukemia (CML) patients, despite their treatment response, cannot be considered cured and must take the treatment indefinitely. Recently, data from different clinical trials have shown how a minority of patients who achieve and maintain a deep molecular response with imatinib, could discontinue the treatment safely. Therefore, treatment free remission (TFR) has been established as a new goal for CML patients. However, at this moment, TFR is only available for a small group of patients, since deep molecular response is achieved in 5 years only in approximately 20% of patients treated with imatinib, and, unfortunately, 50% of patients will eventually relapse. In addition, recent data have shown how a time exposure to imatinib longer than 7 years can be a prognostic factor for TFR. Starting treatment with 2GTKIs (dasatinib, nilotinib and bosutinib) has demonstrated higher probabilities of deep molecular responses. Suppression of the immune system in CML patients at diagnosis is mediated in part by hematopoietic stem cells, which acquire a proliferative/survival advantage and lose the ability to undergo apoptosis. Release of tumor-derived cytokines/chemokines drives the expansion of immune suppressor MDSC and Treg, facilitating downregulation of antitumor effector immunity. PD-L1 is upregulated on CML cells, where it interacts with the co-inhibitory receptor PD-1, and contributes to protection of the malignant cells from immune destruction. MDSC originate from the malignant BCR-ABL1 clone and mediate their suppressive activity via a number of mechanisms, including increased production of reactive oxygen and nitrogen species (NO, ROS), arginase-1, and TGF-β1. MDSC can induce Treg expansion, and Treg also express PD-1 to promote enhanced suppressor function. We know how PD-1 is expressed on T cells at diagnosis in CML patients, and that its expression decreases considerablyafter achieving deep molecular response. The combination of TKI plus interferon has resulted into higher probabilities of deep molecular responses compare to TKI monotherapy in several clinical trials. It is also known how the immune system plays a crucial role in treatment free remission strategies. The lack of overt relapse in patients who have previously achieved a deep molecular response, despite the presence of very low levels of residual disease has been attributed to immunological control of CML. IFN/imatinib induction treatment followed by a temporary IFN maintenance may enable a higher rate of treatment discontinuation in CML patients in at least MMR when stopping. The TIGER study (NCT01657604) is currently investigating de-escalating maintenance therapy using low dose IFN as an inducer of immune surveillance following nilotinib discontinuation.

	Upregulation of the immune checkpoint receptor PD-L1 and its receptors, PD-1 and B7.1, has been demonstrated in peripheral blood mononuclear cells from patients with CML. During the past 5 years, immune checkpoint inhibitors have revolutionized the management and treatment of cancer, because they have been associated with striking improvements in clinical outcomes in patients with some tumor types. Programmed death ligand 1 (PD-L1) is an immune-checkpoint protein expressed on tumor cells and tumor-infiltrating immune cells that downregulates antitumoral T-cell function through binding to programmed death 1 (PD-1) and B7.1 (also known as CD80) receptors. The engineered, humanized IgG1 monoclonal anti-PD-L1 antibody atezolizumab blocks PD-L1–PD-1 and PD-L1–B7.1 interactions, resulting in restoration of antitumor T-cell activity and enhanced T-cell priming. Blocking PD-L1–B7.1 binding on T cells and antigen-presenting cells might additionally inhibit downregulation of immune responses, thus preventing inhibition of T-cell activation and cytokine production. Direct targeting of PD-L1 leaves the PD-L2–PD-1 interaction intact, potentially avoiding effects on immune homoeostasis. Atezolizumab is engineered to eliminate binding to Fc receptors and prevent Fc-effector function. This modification eliminates antibody-dependent cell mediated cytotoxicity and thus avoids potential loss of PD-L1-expressing T-effector cells and reduced anticancer immunity. The combination of bosutinib plus atezolizumab in first line treatment in newly diagnosis chronic-phase CML patients would increase molecular responses and therefore TFR probabilities in these patients. We propose an Open-Label Phase Ib/II Study of Bosutinib in Combination with Atezolizumab for the Treatment of New Diagnosis Chronic Phase-Chronic Myeloid Leukemia Patients.
Study Objectives	**Primary endpoint**: Safety profile of bosutinib 400 mg daily in combination with atezolizumab in participants with chronic myeloid leukemia as first line treatments **Secondary endpoints**: • To evaluate the Major Molecular Response (MMR) and Molecular Response (MR) rates at 3, 6, 12 months and at the End of Treatment (EoT) visit. • Percentage of Participants Alive at Month 6, 12 and the EoT visit. • Number of confirmed MR4 and MR4.5 at end of treatment. • The rate of confirmed MR4 and MR4.5 at the end of treatment. • Number of Complete Cytogenetic Responses (CCyR) [Time Frame: At 1 year] • The rate of Complete Cytogenetic Response (CCyR) at 1 year. • Number of days to response (CCyR, MMR, MR4, MR4.5) [Time Frame: at the EoT visit] • The median time to response and the overall estimated probability of response (CCyR, MMR, MR4, MR4.5). • Number of overall surviving patients [Time Frame: at the EoT visit] • Number of progression-free survival patients [Time Frame: at the EoT visit] • Number of failure-free survival patients [Time Frame at the EoT visit] • Number of event-free survival patients [Time Frame: at the EoT visit] • Immunological Studies
Study Design	This is a phase Ib/II, simple arm, open-label and dose-escalation study designed to determine the safety profile and the recommended phase III dose (RP3D) of bosutinib when administered in combination with atezolizumab in naïve patients with chronic myeloid leukemia in chronic phase. The patients will be divided in two groups, with different start points, and will have three different therapy combinations during the study, which are described below. The first 10 patients included in the study will begin first. If at least 9 of these patients do not suffer DLTs during the first 2 cycles of the combined treatment (bosutinib 400 mg/day plus atezolizumab 840 mg every two weeks), the following 26 patients will be included, otherwise, the study will be terminated.

	– **First therapy** All patients included, both the first 10 patients and the next 26 patients, will receive bosutinib 400 mg/day in monotherapy for one cycle. All patients who tolerate this cycle of bosutinib treatment will continue to the second therapy (bosutinib plus atezolizumab). – **Second Therapy** *<u>Group 1: The first 10 patients included</u> Only for the first ten patients included in the study, atezolizumab will be introduced at a dose of 840 mg every two weeks combined with 400 mg/day of bosutinib for 2 cycles (8 weeks). These patients will be closely monitored for safety issues. If dose-limiting toxicities (DLTs) appear in 2 or more patients the study will end. If no relevant safety issues regarding the combination of drugs is detected the study will continue. These initial 10 patients will cross-over from bosutinib 400 mg/day plus atezolizumab 840 mg every 2 weeks to bosutinib 400 mg/day plus atezolizumab 1680 mg every 4 weeks for 10 cycles (40 weeks). *<u>Group 2: The next 26 patients included</u> After receiving bosutinib 400 mg/day in monotherapy for one cycle (1st therapy), the last 26 patients included will receive bosutinib 400 mg/day plus atezolizumab 1680 mg every 4 weeks for 12 cycles. Patients will be closely monitoring. If DLTs appear in 2 or more patients at a dose of 1680 mg of Atezolizumab every 4 weeks, the dose of atezolizumab will be reduced for all patients to an 840 mg Atezolizumab every 2 weeks dose. All patients completing 12 treatment cycles (48 weeks) will begin the last therapy of study. - **Third Therapy** All patients completing cycle 12 with the combined bosutinib plus atezolizumab therapy will continue with bosutinib 400 mg/day in monotherapy for 12 more cycles. A DLT would include either of the following adverse events occurring during of the bosutinib/atezolizumab therapy and that is considered at least possibly related to bosutinib and/or atezolizumab: • Grade 4 neutropenia (<500/μl) persisting for >7 day duration or Grade 4 white cell count decrease for >7 day duration (<1000/μl). • Febrile neutropenia (ANC<1000/μl and fever ≥38.5°C). • Grade 4 thrombocytopenia >48 hour duration or with bleeding requiring platelet transfusion. • Any Grade 3 or 4 clinically evident non-hematological toxicity • Any ≥Grade 3 toxicity that requires >14 days to resolve (to ≤Grade 1 despite optimal medical therapy). DTLs will be graded according to the NCI CTCAE, v5.0.
Diagnosis and Main Inclusion Criteria	Patients must fulfill the following criteria to be eligible for the study: 1. Male or female patient ≥ 18 years of age. 2. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study. 3. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

	4. Newly Patient with Philadelphia chromosome positive chronic phase CML and BCR-ABL1 transcript detected at diagnosis. 5. ECOG Performance Status of 0, 1, or 2. 6. Adequate hepatic, renal and pancreatic function defined as: a. Total bilirubin within normal range or Direct bilirubin ≤ 1.5 x ULN, b. Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN) or ≤5 x ULN if attributable to liver involvement of leukemia, 7. Women of childbearing potential must have a negative pregnancy test documented prior enrollment. Women of childbearing potential and men must be using an adequate method of contraception.
Exclusion Criteria	Patients eligible for inclusion in the study must not fulfill the following exclusion criteria: 1. Pregnant or lactating women, 2. Participation in another clinical trial with any investigational drug within 30 days prior to study enrollment, 3. Any prior medical treatment for CML, including tyrosine kinase inhibitors (TKIs), with the exception of hydroxyurea, 4. Period of time since CML diagnosis longer than 6 months, 5. Hypersensitivity to the active substances or to any of the excipients of the bosutinib and/or atezolizumab formulations, 6. Major surgery or radiotherapy within 14 days of enrollment, 7. Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, 8. Concomitant use of or need for medications known to prolong the QTc interval, 9. Concomitant use with strong CYP3A inhibitors (ketoconazole, itraconazole, clarithromycin), moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem), or strong CYP3A inducers (rifampin, carbamazepine, phenytoin), 10. History of clinically significant or uncontrolled cardiac disease, including: a. Stage II to IV congestive heart failure (CHF) as determined by the New York Heart Association (NYHA) classification system for heart failure. b. Myocardial infarction within the previous 6 months, c. Symptomatic cardiac arrhythmia requiring treatment, d. Diagnosed or suspected congenital or acquired prolonged QT history or prolonged QTc. (QTcF should not exceed 500 msec), 11. Grade III or IV fluid retention, 12. Uncontrolled hypomagnesemia or uncorrected symptomatic hypokalemia, due to potential effects on the QTc interval, 13. Uncontrolled or symptomatic hypercalcemia, 14. Recent or ongoing clinically significant gastrointestinal (GI) disorder e.g. Crohn's Disease, Ulcerative Colitis or prior total or partial gastrectomy, 15. Autoimmune or infectious active disease that require treatment, 16. CML patient not in chronic phase at diagnosis, 17. Patients with known atypical transcript. An atypical transcript is defined by the presence of any transcript in the absence of the major transcripts b3a2 (e14a2) and b2a2 (e13a2) or p210 protein, 18. Patients with known resistant mutation(s) (T315I, E255K/V, Y253H, F359C/V). It is not necessary to perform mutation tests on the patient to be included in the study if they were not previously performed, 19. Individuals with an active malignancy, 20. Known seropositivity to human immunodeficiency virus (HIV), current acute or chronic hepatitis B (hepatitis B surface-antigen positive) and/or hepatitis C. 21. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug. 22. Patients with severe renal impairment

Number of Patients	36 patients of both genders
Approximate Duration of Patient Participation	Approximately two years with treatment (25 cycles of 28 days).
Approximate Duration of Study	The estimated duration of the clinical trial is approximately 36 months, including 12 months for enrollment and 26 cycles of treatment/follow-up.
Approximate Number of Study Centers	Up to 10 centers; national (Spain).
Dosage Administration	**Group 1**: The first 10 patients: 1. One cycle only with bosutinib 400 mg/day therapy. 2. 2 cycles with bosutinb 400 mg/day plus atezolizumab 840 mg q2w therapy. 3. 10 cycles with bosutinb 400 mg/day plus atezolizumab 1680 mg q4w therapy. 4. 12 cycles with bosutinib 400 mg/day therapy. **Group 2**: The next 26 patients: 1. One cycle only with bosutinib 400 mg/day therapy. 2. 12 cycles with bosutinb 400 mg/day plus atezolizumab 1680 mg q4w therapy. **3.** 12 cycles with bosutinib 400 mg/day therapy.
Efficacy Evaluation	Hematologic response rate, cytogenetic response rate, molecular response rate, and disease progression will be assessed according to standard criteria, as follows: • Bone marrow aspirates for assessment of cytogenetic response every 3 months after initiating bosutinib treatment. After complete cytogenetic response (CCyR) has been achieved, only if there is suspicion of disease progression, • BCR-ABL assessment to determine molecular response every 3 months after initiating bosutinib treatment, • Complete blood count (CBC) for assessment of hematologic response every 3 months, • Survival follow-up.
Safety Evaluation	Safety assessments will include physical and laboratory examinations. AEs will be graded according to the NCI CTCAE, v5.0. All patients receiving at least 1 dose of bosutinib will be considered evaluable for safety. The AE and VOE incidence rates, as well as the frequency of occurrence of overall toxicity -categorized by toxicity grades (severity). Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes clinically significant in laboratory tests over time will be presented.
Statistical Analysis	Statistical analysis and number of patients planned: There will be no formal calculation of the sample size for the study. The sample size is selected to allow sufficient data collection for the DLT and safety assessment. The minimum number of patients for the DLT evaluation will be 10 if no DLT is observed. After MTD is calculated, 26 more patients will be recruited for the dose escalation phase. 36 patients (both, a first group of 10 patients and a second of 26 patients) will receive bosutinib 400 mg/day in monotherapy during one cycle of treatment. According to previous experience (*Tim H Brümmendorf et al, 2015; Jorge E cortes. el al, 2018*), we assume that, at most, 15% of the patients included will not enter the dose escalation phase after the first month of treatment with bosutinib, due to side effects. Consequently, a total of 30-31 patients will receive the combination of bosutinib plus atezolizumab. Data will be analyzed using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), coefficient of variation, median and range as appropriate. The categorical values will be summarized using the number of observations and percentage as appropriate.

	This plan is extensively detailed in “PLANNED STATISTICAL ANALYSIS” of the project.
Study timelines	The first patient first visit (FPFV) is planned for September 2020 and the recruitment period is planned to last 1 year. The data cutoff date will be the date of the last patient last visit (LPLV).
Rationale for Number of Patients	This is a single-arm exploratory study.

6 BACKGROUND

6.1 Chronic Myeloid Leukemia: Pathogenesis and Treatment

Chronic Myeloid Leukemia (CML) is a hematological stem cell disorder associated with a specific chromosomal translocation known as the Philadelphia (Ph) chromosome; it is found in 95% of patients (*Nowell and Hungerford 1960*; *Rowley 1973*). The translocation consists in the fusion of the ABL proto-oncogene with the BCR gene, resulting in the production of an activated form of the ABL protein-tyrosine kinase (*Bartram et al, 1983*; *Heisterkamp et al, 1983*). Expression of the BCR-ABL protein causes leukemia in mice, suggesting this protein is linked to disease pathogenesis (*Daley et al, 1990*; *Kelliher et al, 1990*).

Clinically, CML progresses through three distinct phases of increasing refractoriness to therapy: chronic phase (CP) (median duration 3-4 years; median survival up to 10 years with allogenic bone marrow transplant and 5-6 years with interferon (IFN), accelerated phase (AP) (median duration 3-9 months; median survival 8-18 months), and blast crisis (BC) (median survival 3-6 months) (*Enright & McGlave 2000*). Most patients suffer the CP form, which is characterized by splenomegaly and leukocytosis with generally few symptoms.

National Comprehensive Cancer Network (NCCN) guideline on CML (NCCN guideline v1.2019) (*Radich, 2018*) and European Leukemia Net (ELN) (*Steegmann et al, 2016*) recommend continuing tyrosine kinase inhibitor (TKI) treatment (i.e., imatinib, nilotinib, dasatinib, ponatinib, bosutinib) indefinitely in all responding patients. Treatment discontinuation may be considered in individual patients, also outside studies, if proper, high-quality, and certified monitoring can be ensured at monthly intervals.

Imatinib (IM) rapidly became the gold standard therapy in CML that dramatically changed the prognosis of the disease (*Druker et al., 2006*). More potent second-generation tyrosine-kinase inhibitors (TKI) have been consecutively developed to counteract resistance to IM in a substantial proportion of patients such as dasatinib, nilotinib, bosutinib and ponatinib. Efficacy of second and third generation TKIs was first shown in second-line therapy for patients intolerant or resistant to IM. Superiority of dasatinib and nilotinib over IM was thereafter demonstrated in first-line therapy (DASISION and ENESTnd phase III trials), in terms of achievement of complete cytogenetic response (CCyR) at 12 months and an increased rates of major molecular responses (MMR) and deep molecular responses (*Fujisawa S et al., 2014*; *Larson RA et al., 2012*).

6.2 Overview of Bosutinib

Bosutinib is an oral, once-daily, second-generation tyrosine kinase inhibitor, with a manageable and distinct safety profile. Bosutinib exhibits dose-proportional increases in exposure between 200 and 600 mg, and its absorption increases with food. It has extensive tissue distribution, is highly bound to plasma proteins, and is primarily metabolized in the liver by cytochrome P450 (CYP) 3A4. Hepatic and renal impairment increases the exposure to

bosutinib. Metabolic drug–drug interactions of bosutinib are limited in scope to CYP3A inhibitors and inducers but are significant in their extent. Coadministration of bosutinib with strong or moderate CYP3A inhibitors or inducers should be avoided (*Abbas, 2016*).

Bosutinib is used for the treatment of chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options (*EMA, 2019*).

This indication for bosutinib is based principally on the results of an open-label, single-arm, multicenter, phase 1/phase 2 study in adults with chronic, accelerated, or blast phase CML following therapy with either imatinib alone or imatinib followed by dasatinib and/or nilotinib; patients were intolerant of or had a disease that was resistant to imatinib. In this study, 546 patients received bosutinib 500 mg once daily (increased to 600 mg daily if complete hematologic or cytogenetic response was not achieved by week 8 or 12, respectively). The median duration of therapy with bosutinib was 22 months in patients with chronic phase CML previously treated with only imatinib; patients previously treated with imatinib followed by dasatinib and/or nilotinib received therapy with bosutinib for a median duration of 8 months (*EMA, 2019; FDA, 2019*).

At the time of data analysis, patients with chronic phase CML previously treated with imatinib alone or imatinib followed by dasatinib and/or nilotinib had been followed for at least 23 or 13 months, respectively. The primary efficacy end point of this study was major cytogenetic response (defined as elimination or substantial reduction [by at least 65%] of Ph+ hematopoietic cells) at 24 weeks. In this study, resistance to imatinib was defined as failure to achieve or maintain any hematologic improvement within 4 weeks of therapy; or failure to achieve a complete hematologic response by 3 months, a cytogenetic response by 6 months, or a major cytogenetic response by 12 months; or disease progression after a previous cytogenetic or hematologic response; or evidence of the genetic mutation in the Bcr-Abl gene associated with imatinib resistance. Imatinib intolerance was defined as inability to tolerate imatinib because of toxicity, or disease progression with imatinib and inability to receive a higher dosage because of toxicity. Definitions of resistance and intolerance to both dasatinib and nilotinib were similar to those for imatinib. Major cytogenetic response was achieved at 24 weeks in 34% of patients in chronic phase CML who were previously treated with imatinib alone and in 27% of those previously treated with imatinib followed by dasatinib or nilotinib. At the time of data analysis, median durations of response had not been reached. Disease progression (i.e., transformation from chronic phase to accelerated or blast phase CML) occurred in 4.3% of patients with chronic phase CML. In an exploratory analysis, treatment with bosutinib resulted in confirmed complete hematologic responses at 48 weeks in 30 or 15% of patients in accelerated or blast phase CML, respectively; the median duration of therapy with bosutinib for these patients previously treated with at least imatinib who were in

the accelerated or blast phase of the disease was 10 or 3 months, respectively (*EMA, 2019; FDA, 2019*).

More recently, bosutinib was also authorized in adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) (*EMA, 2019*) based on the results obtained in the BFORE study (*Cortes, 2018a*). In this study bosutinib was compared with imatinib in 536 newly diagnosed CML patients in the 'chronic phase'. The main measure of effectiveness was the number of patients who had a 'major molecular response'. After one year of treatment, 47% (116 out of 246) of patients treated with bosutinib had a major molecular response, compared with 37% (89 out of 241) of patients treated with imatinib.

Diarrhea is the most frequent side effect related to bosutinib in clinical trials (80% any grade, <10% of grade 3–4). This side-effect is usually well-managed with dose reductions/interruptions, since <1% of the patients treated with bosutinib in the BEFORE study discontinued treatment due to diarrhea (*Cortes, 2012; Cortes, 2018b*). In general, pleural effusion is a rare complication in bosutinib treated patients. However, patients who had pleural effusion while on dasatinib and later received bosutinib treatment had a high risk of recurrence of this complication (*Gambacorti, 2018*). Cardiac and vascular toxicity have been evaluated in bosutinib treated patients enrolled in clinic al trials showing a good safety profile. Similar incidences were observed with bosutinib (first or later lines) or comparing to imatinib treated patients (*Cortes, 2016*). A decrease in the glomerular filtration rate has been observed with long-term exposure to bosutinib. Renal AEs were reported in 73/570 patients (13%) receiving bosutinib as a second-line or later treatment, and in 22/248 (9%) receiving bosutinib as first-line treatment (*Cortes, 2017*).

6.3 Overview of Atezolizumab

Atezolizumab is a monoclonal antibody targeting programmed death ligand 1 (PD-L1 or CD274 antigen). PD-L1 is thought to play an important role in suppressing the immune system triggered by disease, by reducing the proliferation of antigenspecific CD8+ T-cells and controlling the accumulation of foreign antigen-specific T-cells. Up-regulation of PD-L1 has been suggested as a mechanism used by cancer cells to evade the host immune system (*Markham, 2016*). Atezolizumab has been approved in Europe (*EMA, 2019*) as monotherapy is for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC):

- after prior platinum containing chemotherapy, or
- who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%.

Also, in combination with bevacizumab, paclitaxel and carboplatin, atezolizumab is indicated for the first-line treatment of adult patients with metastatic non-squamous non small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, atezolizumab, in

combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.

Atezolizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK positive NSLCLC should also have received targeted therapy before receiving atezolizumab.

Atezolizumab at a dose of 1–20 mg/kg produced a dose-proportional increase in exposure to the drug. Typical clearance was 0.20 L/day, volume of distribution at steady state was 6.9 L, and the terminal half-life was 27 days, according to a population analysis of patients in the dose range (n = 472). This population analysis also suggested steady state occurs after 6–9 weeks treatment (2–3 dosage cycles). Systemic accumulation in terms of area under the plasma concentration time curve (AUC), maximum concentration (Cmax) and trough concentration (Cmin) was 1.91, 1.46 and 2.75-fold, respectively. The systemic exposure to atezolizumab was not significantly affected when analysed according to patient age, body-weight, gender, positive anti-therapeutic antibody status, albumin levels, tumour burden, region or race, mild or moderate renal impairment, mild hepatic impairment, level of PD-L1 expression, or Eastern Cooperative Oncology Group (ECOG) performance status. The potential for atezolizumab to interact with other drugs is unknown (*Markham, 2016; EMA, 2019*).

Major common AEs involved fatigue, decreased appetite, nausea, diarrhea, pyrexia, pruritus, cough, edema peripheral, and rash. The most common severe AEs were fatigue, anemia, and dyspnea. The overall atezolizumab-related death rate was much lower than chemotherapeutics-related death rate. Atezolizumab has better overall survival and lower risk of AEs compared with chemotherapy (*Tie, 2019*).

7 STUDY RATIONALE AND PURPOSE

Since the introduction of imatinib and subsequent second generation tyrosine kinase inhibitors (2GTKIs), the prognosis of chronic-phase Chronic Myeloid Leukemia (CP-CML) has improved greatly. Initially considered to be a lethal disease with a median estimated overall survival (OS) of 3.2 years, CP-CML is now regarded as a chronic disease with a life expectancy similar to that of the healthy population. However, CML patients, despite their treatment response, cannot be considered cured and should take the treatment indefinitely.

Recently, data from different clinical trials have shown how a minority of patients who achieve a deep molecular response with imatinib and maintain the response, could stop treatment safety. Therefore, treatment free remission (TFR) has been established as a new goal for CML patients. However, currently, TFR is only available for a small group of patients since deep molecular response is achieved by 5 years only in approximately 20% of patients treated with imatinib, and unfortunately, 50% of patients will eventually relapse. In addition, recent data have shown a time exposure to imatinib longer than 7 years as a prognostic factor for TFR.

Starting treatment with 2GTKIS (dasatinib, nilotinib and bosutinib) have demonstrated higher probabilities of deep molecular responses.

Suppression of the immune system in CML patients at diagnosis is mediated in part by hematopoietic stem cells, which acquire a proliferative/survival advantage and lose the ability to undergo apoptosis. Release of tumor-derived cytokines/chemokines drives the expansion of immune suppressor MDSC and Treg, facilitating downregulation of antitumor effector immunity. PD-L1 is upregulated on CML cells, where it interacts with the co-inhibitory receptor PD-1, and contributes to protection of the malignant cells from immune destruction. MDSC originate from the malignant BCR-ABL1 clone and mediate their suppressive activity via a number of mechanisms, including increased production of reactive oxygen and nitrogen species (NO, ROS), arginase-1, and TGF-β1. MDSC can induce Treg expansion, and Treg also express PD-1 to promote enhanced suppressor function. We know how PD-1 is expressed at diagnosis in CML patients on T cells, and that its expression considerable decreases after achieving deep molecular response. The combination of TKI plus interferon has translated into higher probabilities of deep molecular responses compared to TKI monotherapy in several clinical trials.

It is also known how the immune system plays a crucial role in treatment free remission strategies. The lack of overt relapse in patients who have previously achieved a deep molecular response, despite the presence of very low levels of residual disease has been attributed to immunological control of CML. IFN/imatinib induction treatment followed by a temporary IFN maintenance may enable a higher rate of treatment discontinuation in CML patients in at least MMR when stopping. The TIGER study (NCT01657604) is currently investigating de-escalating maintenance therapy using low dose IFN as an inducer of immune surveillance following nilotinib discontinuation.

Upregulation of the immune checkpoint receptor PD-L1 and its receptors, PD-1 and B7.1, has been demonstrated in peripheral blood mononuclear cells from patients with CML.

During the past 5 years, immune checkpoint inhibitors have revolutionized the management and treatment of cancer, because they have been associated with striking improvements in clinical outcomes in patients with some tumor types.

Programmed Death Ligand 1 (PD-L1) is an immune-checkpoint protein expressed on tumor cells and tumor-infiltrating immune cells that downregulates antitumoral T-cell function through binding to programmed death 1 (PD-1) and B7.1 (also known as CD80) receptors. The engineered, humanized IgG1 monoclonal anti-PD-L1 antibody atezolizumab blocks PD-L1–PD-1 and PD-L1–B7.1 interactions, resulting in restoration of antitumor T-cell activity and enhanced T-cell priming. Blocking PD-L1–B7.1 binding on T cells and antigen-presenting cells might additionally inhibit downregulation of immune responses, thus preventing inhibition of T-cell activation and cytokine production. Direct targeting of PD-L1 leaves the PD-L2–PD-1 interaction intact, potentially avoiding effects on immune homoeostasis. Atezolizumab is engineered to eliminate binding to Fc receptors and to prevent Fc-effector function. This

modification eliminates antibody-dependent cell mediated cytotoxicity and thus avoids potential loss of PD-L1-expressing T-effector cells and reduced anticancer immunity.

The combination of bosutinib plus atezolizumab in first line CML chronic phase patients would increase molecular responses and therefore TFR probabilities in newly diagnosed CML patients.

8 STUDY OBJECTIVE

8.1 Primary Objective

The primary objective is to evaluate the safety profile of bosutinib 400mg/day in combination with atezolizumab as a first line treatment in participants with chronic phase-chronic myeloid leukemia.

8.2 Secondary Objectives

- To evaluate the Major Molecular Response (MMR) and Molecular Response (MR) rates at 3, 6, 12 months and at the End of Treatment (EoT) visit. Based on:
  - MMR is defined as ≥ 3-log reduction in BCR-ABL transcripts or a ratio of ≤ 0.1% on the International Scale (IS)
  - Molecular Response (MR): As defined in section 4. Definition of Terms
- Percentage of participants alive at months 6 and 12 and at the EoT visit.
- Number of confirmed MR4 and MR4.5 at end of treatment.
- The rate of confirmed MR4 and MR4.5 at the end of treatment.
- Number of Complete Cytogenetic Responses (CCyR) at 1 year]
- The rate of Complete Cytogenetic Response (CCyR) at 1 year.
- Number of days to response (CCyR, MMR, MR4, MR4.5). [Time Frame: at the EoT visit]
- The median time to response and the overall estimated probability of response (CCyR, MMR, MR4, MR4.5).
- Number of overall surviving patients [Time Frame: at the EoT visit]
- Number of progression-free survival patients.[Time Frame: at the EoT visit]
- Number of failure-free survival patients. [Time Frame at the EoT visit]
- Number of event-free survival patients. [Time Frame: at the EoT visit]
- Immunological Studies

9 STUDY DESIGN

This is a phase Ib/II, two arms, open-label and dose-escalation study designed to determine the safety profile and the recommended phase III dose (RP3D) of bosutinib when administered in combination with atezolizumab in naïve patients with chronic myeloid leukemia in chronic phase. This study has two groups of patients (Figure 1).

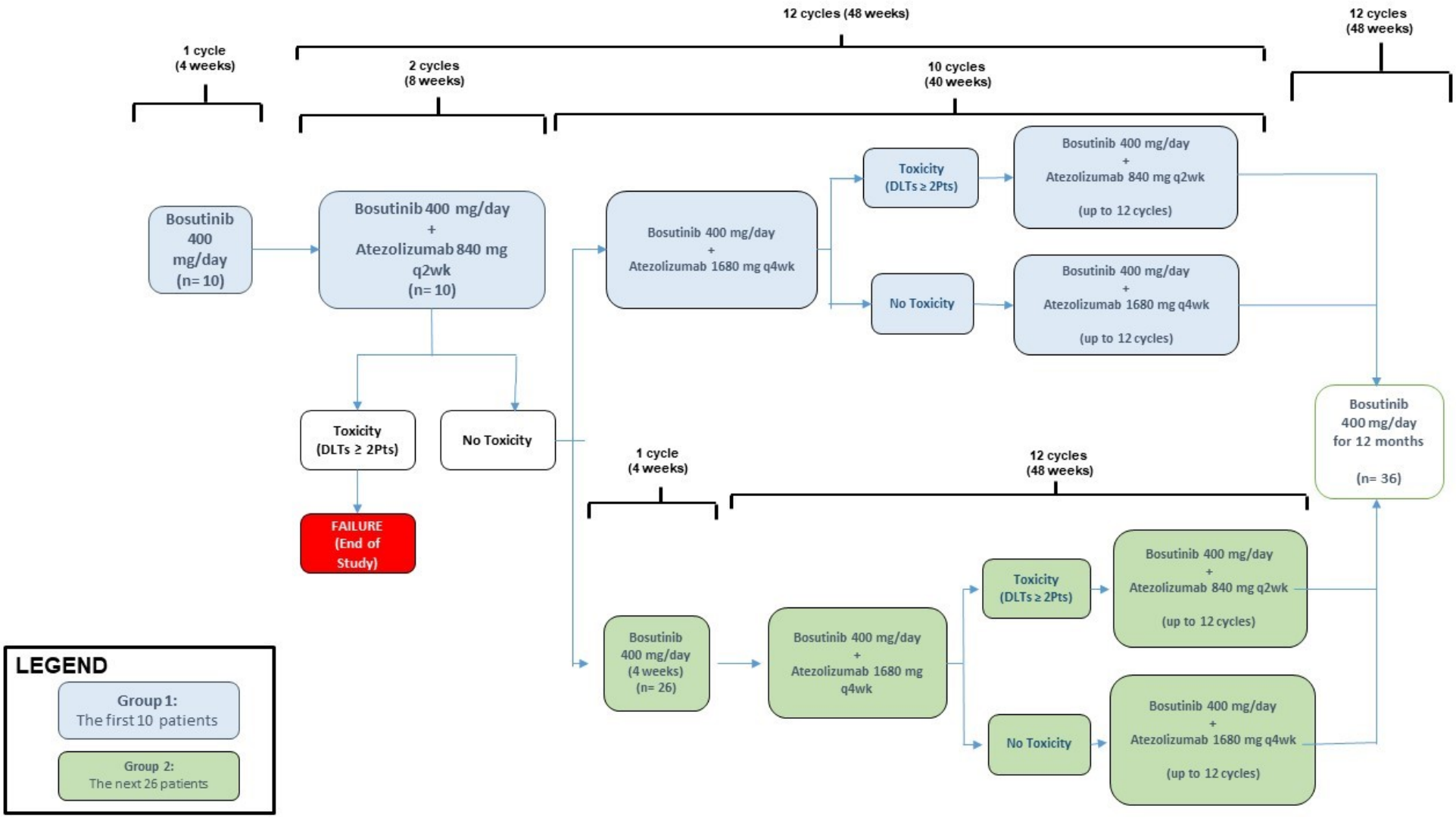
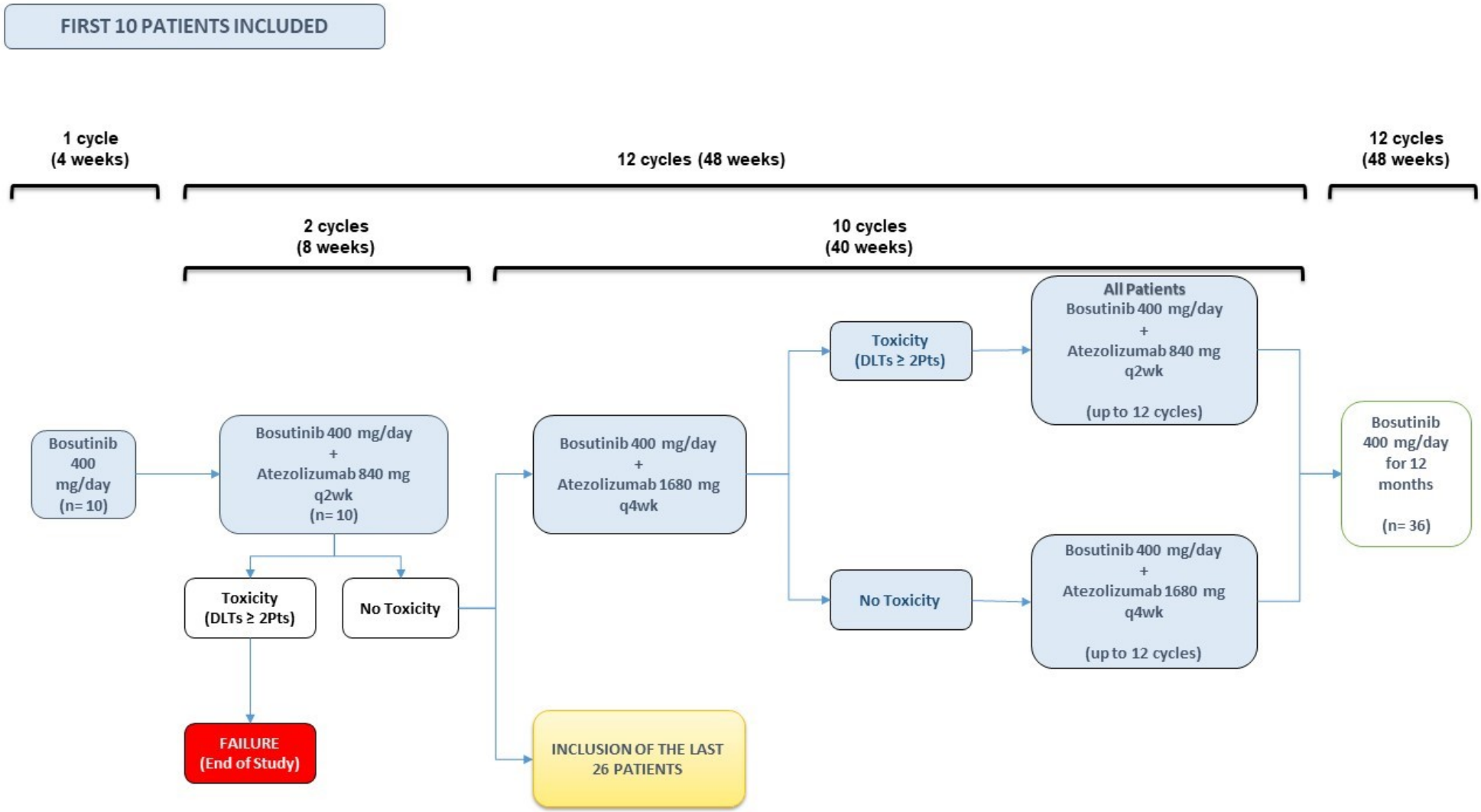
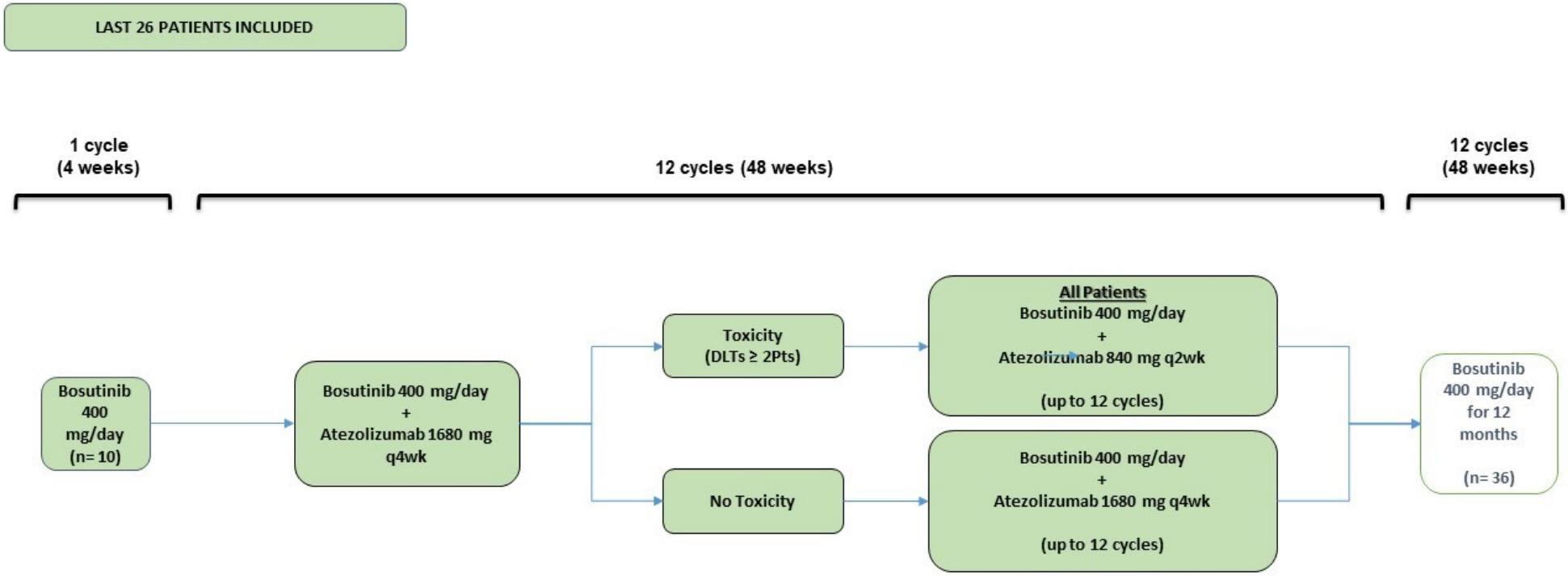

1 cycle
(4 weeks)
2 cycles
(8 weeks)
10 cycles
(40 weeks)
12 cycles (48 weeks)
12 cycles
(48 weeks)
Bosutinib
400
mg/day
(n= 10)
Bosutinib 400 mg/day
+
Atezolizumab 840 mg
q2wk
(n= 10)
Toxicity
(DLTs ≥ 2Pts)
No Toxicity
FAILURE
(End of
Study)
Bosutinib 400 mg/day
+
Atezolizumab 1680 mg q4wk
Toxicity
(DLTs ≥ 2Pts)
Bosutinib 400 mg/day
+
Atezolizumab 840 mg q2wk
(up to 12 cycles)
No Toxicity
Bosutinib 400 mg/day
+
Atezolizumab 1680 mg q4wk
(up to 12 cycles)
Bosutinib
400 mg/day
for 12 months
(n= 36)
1 cycle
(4 weeks)
12 cycles
(48 weeks)
Bosutinib
400 mg/day
(4 weeks)
(n= 26)
Bosutinib 400 mg/day
+
Atezolizumab 1680 mg
q4wk
Toxicity
(DLTs ≥ 2Pts)
Bosutinib 400 mg/day
+
Atezolizumab 840 mg q2wk
(up to 12 cycles)
No Toxicity
Bosutinib 400 mg/day
+
Atezolizumab 1680 mg q4wk
(up to 12 cycles)
LEGEND
Group 1:
The first 10 patients
Group 2:
The next 26 patients

Figure 1. Chronogram of the study




LAST 26 PATIENTS INCLUDED
1 cycle
(4 weeks)
12 cycles (48 weeks)
12 cycles
(48 weeks)
Bosutinib 400 mg/day (n= 10)
Bosutinib 400 mg/day + Atezolizumab 1680 mg q4wk
Toxicity (DLTs ≥ 2Pts)
No Toxicity
All Patients
Bosutinib 400 mg/day + Atezolizumab 840 mg q2wk (up to 12 cycles)
Bosutinib 400 mg/day + Atezolizumab 1680 mg q4wk (up to 12 cycles)
Bosutinib 400 mg/day for 12 months (n= 36)

9.1 Patient Screening

This study will be conducted on those naïve patients with chronic-phase Chronic Myeloid Leukemia (CP-CML) who meet the established selection criteria (see below). The patients that sign the IC and meet the selection criteria will be selected to enter the study.

Results of all screening evaluations must be reviewed by the Principal Investigator or his/her designee prior to the enrollment of a patient into the study to assure that all inclusion and none exclusion criteria have been satisfied.

All study patients must be thoroughly informed about all aspects of the study, including the study visit schedule and required assessments for informed consent. The written informed consent must be obtained prior to any screening evaluations. If a patient is unable to read, an impartial witness should be present during the entire informed consent discussion.

This is an open label clinical trial, and no randomization or blinding procedures are required.

The patients will be divided in two groups, with different start points, and will have three different therapy combinations during the study, which are described below. The first 10 patients included in the study will begin first. If at least 9 of these patients do not suffer DLTs during the first 2 cycles of the combined treatment (bosutinib 400 mg/day plus atezolizumab 840 mg every two weeks), the following 26 patients will be included, otherwise, the study will be terminated.

9.2 First therapy

All patients included, both the first 10 patients and the next 26 patients, will receive bosutinib 400 mg/day in monotherapy during one cycle of treatment. All patients who tolerate this cycle of bosutinib treatment will continue to the second therapy (bosutinib plus atezolizumab).

9.3 Second Therapy

9.3.1 Group 1: The first 10 patients

Only for the first ten patients included in the study, atezolizumab will be introduced at a dose of 840 mg every two weeks combined with 400 mg/day of bosutinib for 2 cycles (8 weeks). These patients will be closely monitored for safety issues.

If dose-limiting toxicities (DLTs) appear in 2 or more patients the study will end.

A DLT would include either of the following adverse events that occurred during bosutinib therapy in combination with atezolizumab, if it is considered at least possibly related to bosutinib and/or atezolizumab:

- Grade 4 neutropenia (<500/μl) persisting for > 7 day duration or Grade 4 white cell count decrease for >7 day duration (<1000/μl).
- Febrile neutropenia (ANC<1000/ μl and fever ≥38.5°C).

- Grade 4 thrombocytopenia > 48 hour duration or with bleeding requiring platelet transfusion.
- Any Grade 3 or 4 clinically evident non-hematological toxicity.
- Any ≥Grade 3 toxicity that requires >14 days to resolve (to ≤Grade 1 despite optimal medical therapy).

DTLs will be graded according to the NCI CTCAE, v5.0.

If no relevant safety issue, regarding the combination is detected the study will continue.

These initial 10 patients will cross-over from bosutinib 400 mg/day plus atezolizumab 840 mg every 2 weeks to bosutinib 400 mg/day plus atezolizumab 1680 mg every 4 weeks for 10 cycles (40 weeks).

9.3.2 Group 2: The next 26 patients

After receiving bosutinib 400 mg/day in monotherapy for one cycle (1st therapy), the last 26 patients included will receive bosutinib 400 mg/day plus atezolizumab 1680 mg every 4 weeks for 12 cycles.

Patients will continue to be closely monitoring. If DLTs appear in 2 or more patients at a dose of 1680 mg of Atezolizumab every 4 weeks, the dose of atezolizumab will be reduced for all patients to an 840 mg Atezolizumab every 2 weeks dose.

All patients completing 12 treatment cycles (48 weeks) will begin the last therapy of study.

9.4 Third Therapy

All patients completing cycle 12 with bosutinib plus atezolizumab therapy will continue with bosutinib 400 mg/day in monotherapy for 12 more cycles.

9.5 Withdrawal criteria

Patients may suspend their participation in the study whenever they wish, based on his/her own judgement and opinion, without giving any explanation, although the investigator may investigate the reasons of a voluntary dropout.

The investigator may also decide to withdraw a patient from the trial if he/she does not comply with the protocol, due to AEs or treatment inefficacy or toxicity.

Patients who do not comply with at least 70% of the scheduled doses of bosutinib or that, in 4 or more times, the administration of atezolizumab is cancelled, will be withdrawn from the study.

10 POPULATION

10.1 Patient Population

The target population of this study includes naïve adult patients of both genders with chronic myeloid leukemia in chronic phase.

10.2 Inclusion Criteria

Patients eligible for inclusion in this study have fulfill the following criteria:

1. Male or female patient ≥ 18 years of age.
2. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study.
3. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
4. Newly Patient with Philadelphia chromosome positive chronic phase CML and BCR-ABL1 transcript detected at diagnosis.
5. ECOG Performance Status of 0, 1, or 2.
6. Adequate hepatic, renal and pancreatic function defined as:
    a. Total bilirubin within normal range or Direct bilirubin ≤ 1.5 x ULN,
    b. Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN) or ≤5 x ULN if attributable to liver involvement of leukemia,
7. Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential). A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy (CTFG, 21/09/2020). These women, must have a negative serum or urine pregnancy test before initiation of study treatment and must also use highly effective methods of contraception while enrolled in the study. The use of highly effective contraception should continue for at least 14 days after the last dose of study treatment. Acceptable forms of highly effective contraception methods include (CTFG, 21/09/2020):

    a. Total abstinence [when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]

    b. Male/female sterilization. These defined as:

        - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment.

          In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed and documented by follow-up hormone level assessment.

- Male sterilization (at least 6 months prior to screening). For female patients on the study, study participation assumes the vasectomized male partner is the sole partner for that patient.

c. Contraceptive methods:

i. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal or transdermal.

ii. Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable or implantable.

iii. Placement of an intrauterine device (IUD) or intrauterine system (IUS).

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy with or without hysterectomy or tubal ligation at least six weeks prior to enrolling. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

If a study patient gets pregnant or is suspected of being pregnant during the study or within 30 days as part of safety evaluations after the final dose of bosutinib, the study Doctor needs to be informed immediately and any ongoing study treatment with bosutinib has to be stopped immediately.

10.3 Exclusion Criteria

Patients eligible for this study must not fulfill the following criteria:

1. Pregnant or lactating women,
2. Participation in another clinical trial with any investigational drug within 30 days prior to study enrollment,
3. Any prior medical treatment for CML including tyrosine kinase inhibitors (TKIs) with the exception of hydroxyurea,
4. Period of time since CML diagnosis longer than 6 months,
5. Hypersensitivity to the active substances or to any of the excipients of the bosutinib and/or atezolizumab formulations,
6. Major surgery or radiotherapy within 14 days of enrollment,
7. Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease,
8. Concomitant use of or need for medications known to prolong the QT interval,

9. Concomitant use with strong CYP3A inhibitors (ketoconazole, itraconazole, clarithromycin), moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem), or strong CYP3A inducers (rifampin, carbamazepine, phenytoin),
10. History of clinically significant or uncontrolled cardiac disease, including:
    a. Stage II to IV congestive heart failure (CHF) as determined by the New York Heart Association (NYHA) classification system for heart failure,
    b. Myocardial infarction within the previous 6 months,
    c. Symptomatic cardiac arrhythmia requiring treatment,
    d. Diagnosed or suspected congenital or acquired prolonged QT history or prolonged QTc. (QTcF should not exceed 500 msec.),
11. Grade III or IV fluid retention,
12. Uncontrolled hypomagnesemia or uncorrected symptomatic hypokalemia, due to potential effects on the QT interval,
13. Uncontrolled or symptomatic hypercalcemia,
14. Recent or ongoing clinically significant gastrointestinal (GI) disorder e.g. Crohn's Disease, Ulcerative Colitis or prior total or partial gastrectomy,
15. Autoimmune or infectious active disease that require treatment,
16. CML patient not in chronic phase at diagnosis,
17. Patients with known atypical transcript. An atypical transcript is defined by the presence of any transcript in the absence of the major transcripts b3a2 (e14a2) and b2a2 (e13a2) or p210 protein,
18. Patients with known resistant mutation(s) (T315I, E255K/V, Y253H, F359C/V). It is not necessary to perform mutation tests on the patient to be included in the study if they were not previously performed,
19. Individuals with an active malignancy,
20. Known seropositivity to human immunodeficiency virus (HIV), current acute or chronic hepatitis B (hepatitis B surface-antigen positive) and/or hepatitis C,
21. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug,
22. Patients with severe renal impairment.

11 TREATMENT

11.1 Study Treatment

Study treatments: Bosutinib (400 mg/day orally)

Atezolizumab (840 mg q2wk or 1680 mg q4wk)

Study drugs: Bosutinib (Bosulif® 100 mg film-coated tablets, Pfizer S.L.U.)

Yellow oval (width: 5.6 mm; length: 10.7 mm) biconvex, film-coated tablet debossed with “Pfizer” on one side and “100” on the other side. Each tablet contains 100 mg bosutinib (as monohydrate).

Bosutinib (Bosulif® 400 mg film-coated tablets, Pfizer S.L.U.)

Orange oval (width: 8.8 mm; length: 16.9 mm) biconvex, film-coated tablet debossed with “Pfizer” on one side and “400” on the other side. Each tablet contains 400 mg bosutinib (as monohydrate).

Atezolizumab (Tecentriq 840 mg concentrate for solution for infusion, Roche Registration GmbH)

Bosutinib study drug will be provided by Pfizer Europe MA EEIG and Atezolizumab will be provided by Roche Registration GmbH.

Patients will receive bosutinib at 400 mg/day orally. Bosutinib will be self-administered by the patient on a daily schedule.

Atezolizumab should be given intravenously in the site. If the first infusion is tolerated (intravenously administration over 60 minutes), all subsequent infusions may be delivered over 30 minutes. Patients will receive atezolizumab 840 mg q2w or 1680 mg q4w. Each 28-days (4 weeks) is referred to as 1 cycle.

Study treatments will be provided only to eligible patients at qualified centers.

11.2 Treatment Administration

11.2.1 Bosutinib Treatment

Patients will take the prescribed 4 tablets of 100 mg or 1 tablet of 400 mg of bosutinib with water and food, at approximately the same time each day (preferably in the morning).

Patients who forget to take their dose more than 12 hours after it is due, should not make up the missed dose. Any missing doses should be recorded, and subsequent training of patients should be documented in the appropriate source record (e.g. clinic chart).

The day that atezolizumab is administered; the patients will take the corresponding dose of bosutinib after the administration of atezolizumab.

A diary card or equivalent where the date and time of administration will be recorded will be provided to the patients.

11.2.2 Atezolizumab Treatment

For the administration of atezolizumab the patient will go to the hospital, in scheduled visit, and will receive 840 mg or 1680 mg, the two therapeutic options available in this study. If the dose is 840 mg, the patient will receive atezolizumab 840 mg every 2 weeks in each cycle, at the beginning of the first day of the cycle, while if the dose is 1680 mg the patient will receive atezolizumab 1680 mg on the first day of cycle (every 4 weeks). The initial dose of atezolizumab must be administered over 60 minutes; if the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

11.3 Formulation, Packaging, and Labeling

11.3.1 Bosutinib Treatment

Bosutinib investigational drug product is supplied as tablets. Each tablet contains either 100 mg or 400 mg of bosutinib as active ingredient. Other ingredients are typical pharmaceutical excipients: in tablet core [Microcrystalline cellulose (E460), Croscarmellose sodium (E468), Poloxamer 188, Povidone (E1201), Magnesium stearate (E470b)] and in film coating [Polyvinyl alcohol; Titanium dioxide (E171); Macrogol 3350; Talc (E553b); Iron oxide yellow (E172), Iron oxide red (E172) (only in the 400 mg tablets]. Tablets will be supplied as follows:

- **White opaque 3-ply PVC/Polychlorotrifluoroethene/PVC blister sealed with push-through foil backing containing either 14 or 15 tablets per blister (2 blisters in each package).**

Carton labels will bear the appropriate label text as required by governing regulatory agencies. Such text will include, at least, product name, product strength, number of tablets, lot number and expiration date.

Bosutinib will not be dosed by weight or body surface area.

11.3.2 Atezolizumab Treatment

Atezolizumab investigational drug product is supplied as a concentrate solution for infusion. Each vial of concentrate contains 840 mg of atezolizumab (Atezolizumab is an Fc-engineered, humanized IgG_1 anti-programmed death-ligand 1 [PD-L1] monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology). Other ingredients are typical pharmaceutical excipients: L-histidine, Glacial acetic acid, Sucrose, Polysorbate 20, and Water for injections. Vials will be supplied as follows:

- Vial of 840 mg: Type I glass vial with a butyl rubber stopper and an aluminum seal with a plastic, grey flip-off cap containing 14 mL of concentrate for solution for infusion.

Carton and vial labels will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, number of tablets, lot number and expiration date.

Atezolizumab will not be dosed by weight or body surface area.

11.4 Treatment Storage, Dispensing, and Accountability

All investigational treatment is to be stored in a secure locked area while under the responsibility of the principal investigator. An authorized person at the investigator's site must record receipt and dispensing of investigational treatments.

The study pharmacist or designee at the investigative site will be responsible for handling and dispensing study drug and completing associated documentary paperwork.

The Investigator will confirm receipt of the investigational product in writing (date and storage conditions).

Supplies will be shipped to the investigative site at appropriate intervals, depending on patient accrual. The site must use either an appropriate dispensing log/accountability form provided by the sponsor or an acceptable substitute. Each time study medication(s) is dispensed for a patient, the following information is recommended to be recorded: the patient's study number, tablet and vial strength, the number of tablets (with the corresponding lot number) and vials dispensed, and the initials of the person dispensing the drug. These logs are to be maintained by the study investigator and will be periodically verified by a representative of the sponsor. The principal investigator is responsible for ensuring that the patient diary card(s) and study drug provided to the patient and returned from the patient are accounted for and noted in source documentation.

The responsible CRA will check the drug supply for inventory purposes and to ensure proper storage at regular intervals throughout the study.

11.4.1 Bosutinib Treatment

The recommended storage condition for bosutinib is ≤ 30°C.

Patients will receive bosutinib at 400 mg/day orally. Bosutinib will be self-administered by the patient on a daily schedule.

The investigator will dispense the bosutinib to the patients every 3 cycles, starting at the time when the patient is included in the clinical trial. Patients will have sufficient medication to continue treatment until the next dispensed medication-visit is scheduled, even if it takes place out of visit the window of plus 14 days. Unused medication and empty blister cards should be returned to the site at dispensed medication-visits and will not be dispensed again.

11.4.2 Atezolizumab Treatment

Atezolizumab must be stored in a refrigerator (2 °C – 8 °C).

Patients will receive an intravenous dose of 840 mg of atezolizumab every 2 weeks or 1680 mg every 4 weeks administrated by the investigator in the site.

The first infusion of Atezolizumab should be given intravenously over 60 minutes. If this infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

11.5 Treatment Duration

The patients included will remain in the study for at least 100 weeks, 4 weeks (1 cycle) in the first treatment phase, 48 weeks (12 cycles) in the second treatment phase, and 48 weeks (12 cycles) in the third treatment phase), unless discontinue early.

The First 10 Patients:

- First cycle, they will receive bosutinib 400 mg/day in monotherapy.
- Second and third cycles, they will receive bosutinib 400 mg/day in combination with atezolizumab 840 mg every two weeks.
- If no safety issues are detected, these patients will cross-over from bosutinib 400 mg/day plus atezolizumab 840 mg every 2 weeks to bosutinib 400 mg/day plus atezolizumab 1680 mg every 4 weeks for 10 more cycles.
- After 12 cycles of treatment with bosutinib plus atezolizumab combination, the patients will continue with bosutinib 400 mg/day in monotherapy for 12 more cycles.

Other 26 Patients:

- First cycle, they will receive bosutinib 400 mg/day in monotherapy.
- Second cycle, they will receive bosutinib 400 mg/day plus atezolizumab 1680 mg every 4 weeks for 12 cycles.
- After 12 cycles of treatment with bosutinib plus atezolizumab combination, the patients will continue with bosutinib 400 mg/day in monotherapy for 12 more cycles.

If, at any point during the treatment with bosutinib 400 mg/day plus atezolizumab 1680 mg every 4 weeks, 2 or more patients experience DLTs, atezolizumab dosage will change to 840 mg every 2 weeks.

11.6 Dose Modification and Dose Delay

The following section summarizes dosing modifications of bosutinib or atezolizumab to manage possible toxicity. Administration of bosutinib or atezolizumab could be stopped for an individual subject in the event of a treatment-related toxicity that, in the Investigator's assessment, warrants discontinuation. Exceptions to these guidelines will require approval from the Medical Monitor.

A maximum discontinuation of 1 month is allowed for the treatment with bosutinib if required due to the onset of adverse events, investigator decision, of other major circumstances. If a subject discontinued treatment for more than one month he/she will be withdrawn from the study and the appropriate follow-up procedures will be conducted. Also, to be included in the

efficacy analysis (Per protocol set population), a subject must comply with at least 70% of treatment with bosutinib. Regarding atezolizumab treatment, fail to administrate up to 3 out of the 11 administrations scheduled, will be allowed to continue in the study. If, for any reason, atezolizumab could not be administered 4 or more times during the course of the study, the subject will be withdrawn from the study and the appropriate follow-up procedures will be conducted. All deviations from the scheduled treatments regime shall be recorded in the patients' clinical history and the eCRF and explained if required.

11.6.1 Dose reduction steps for bosutinib

In case of a toxicity event possibly related to bosutinib, a dose reduction from 400 mg to 300 mg, unless the toxicity resolves (Grade ≤1) is permitted. If a patient requires a second dose reduction from 300 mg to 200 mg, the Investigator should contact the Sponsor to determine if the patient may continue on treatment at a lower dose. The second dose reduction must be approved by the sponsor and will only be considered if the patient in question displays optimum response to bosutinib treatment at the time-point at which the dose reduction is being considered. Patients should remain on the 200 mg dose for a maximum of 4 weeks or until the toxicity resolves, whichever is sooner. In line with the dose reduction and dose escalation guidelines detailed, the dose can then be re-escalated following the escalation guidelines. Any patient on the 200 mg dose with ongoing toxicity after the 4-week point will be discontinued from treatment and will continue with Follow-up evaluations. Dose reductions of bosutinib below 200 mg will not be permitted.

If the Investigator and the Sponsor decide that it is not in the best interest of the patient to remain on treatment at a dose lower than 300 mg/day, the patient will be discontinued from treatment and will continue with Follow-up evaluations.

Once the dose has been reduced for a patient, the patient should remain on that dose unless the toxicity resolves (Grade ≤1). In that case, the dose can be escalated to the previous starting dose.

11.6.1.1 Management of Non-Hematologic Treatment-Related Toxicities

The management of non-hematologic treatment-related toxicities is summarized in Table 1.

Table 1. Non-Hematologic Treatment-Related Toxicities

Adverse Event	**Action**
Elevated liver transaminases	If elevations in liver transaminases (ALT, AST) > 5 × institutional upper limit of normal (ULN) occur, bosutinib should be interrupted until recovery to ≤ 2.5×ULN and may be resumed at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinuation of bosutinib should be considered. If transaminase elevations ≥3×ULN occur concurrently with bilirubin elevations >2×ULN and alkaline phosphatase <2×ULN, bosutinib should be discontinued.
Diarrhea	For Grade 3/4 diarrhea, bosutinib should be interrupted and may be resumed at 400 mg once daily upon recovery to Grade ≤ 1.
Grade 1	Current dose level

Grade 2	For persistent clinically relevant toxicity[b] not responding to optimal management: Temporarily interrupt treatment, and reintroduce at the same dose or reduce dose by 1 level upon recovery to Grade ≤1 within 4 weeks of stopping test article.
Grade 3 [a]	For persistent clinically relevant toxicity[b] not responding to optimal management: Withhold treatment, then dose reduce by 1 level upon recovery to Grade ≤1within 4 weeks of stopping test article. If recovery takes longer than 4 weeks, the Investigator should contact the Sponsor to determine if the patient may continue on treatment.
Grade 4 [a]	Withhold treatment. Investigator and Sponsor to review to determine if patient may continue on treatment with appropriate dose reduction.

a. For patients requiring dose reduction due to toxicity, who have been free of the toxicity (Grade ≤ 1) for at least 1 month and are otherwise tolerating study drug, the Investigator may choose to re-escalate dose by 1 dose level back to starting dose.

b. Persistent Clinically Relevant Toxicity is defined as - symptoms of toxicity which, despite optimal medical management, persist for ≥ 14 days ("persistent") and cause sufficient symptoms or signs of illness in the subject to warrant further intervention, i.e. dose adjustment ("clinically relevant").

Subjects with Grade 3 non-hematological toxicity that does not respond to optimal management, will be managed by withholding treatment, followed by dose reduction by 1 level upon recovery to Grade ≤ 1. If, on re-challenge at reduced dose, the subject remains free of toxicity (Grade ≤ 1) for at least 1 month, the Investigator may choose to re-escalate the dose by 1 level back to the starting dose.

11.6.1.2 Hematologic Treatment-Related Toxicity

Dose reductions are recommended for severe or persistent neutropenia and thrombocytopenia. The management of hematologic treatment-related toxicities is summarized in Table 2.

Table 2. Hematologic Treatment-Related Toxicity

Adverse Event	**Action**
Grade 1	Current dose level
Grade 2	Current dose level
Grade 3 [a]	Withhold treatment: If recovered to Grade ≤2 within 2 weeks of treatment hold: re-introduce study drug at same dose. If recovered within 4 weeks of treatment hold: reduce study drug by 1 dose level. At subsequent occurrences of Grade 3 toxicity, dose must be reduced upon recovery to Grade ≤2. If recovery takes longer than 4 weeks, the Investigator should contact the Sponsor to determine if the patient may continue on treatment.
Grade 4 [a]	Withhold treatment. Investigator and Sponsor to review to determine if patient may continue on treatment with appropriate dose reduction.

a. For patients requiring dose reduction due to toxicity, who have been free of the toxicity (Grade ≤ 1) for at least 1 month and are otherwise tolerating study drug, the Investigator may choose to re-escalate dose by 1 dose level back to starting dose

Subjects fulfilling criteria for dose escalation due to suboptimal response, but also exhibiting Grade 2 hematologic treatment related toxicity will be eligible for dose escalation; however, if hematologic toxicity increases to Grade 3 or 4 after dose escalation, the subject will be managed as per the instructions for Grade 3 or 4 hematological toxicities in Table 2.

11.6.2 Dose reduction steps for atezolizumab

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect and, in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit-risk balance a given subject may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in subjects with life-threatening, immune-mediated adverse events. Specific guidelines for immune-mediated events are provided in Tables 3 to 13.

For all other non-immune mediated adverse events, including infections, atezolizumab should be withheld for Grade 3 or higher toxicity with the following exceptions:

- Grade 3 nausea that responds to antiemetic treatment within 7 days
- Grade 3 vomiting that responds to antiemetic treatment within 7 days
- Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
- Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of atezolizumab
- Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of atezolizumab

Administration of atezolizumab may be restarted upon recovery from toxicity to Grade 1 or baseline.

11.6.2.1 Pulmonary Events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab.

All pulmonary events should be thoroughly evaluated, as follows, for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. For specific management guidelines, please see table 3.

Table 3. Management Guidelines for Pulmonary Events, including pneumonitis

Adverse Event	Management
Pulmonary event, Grade 1	▪ Continue atezolizumab and monitor closely. ▪ Re-evaluate on serial imaging. ▪ Consider subject referral to pulmonary specialist.
Pulmonary event, Grade 2	▪ Withhold atezolizumab for up to 12 weeks after event onset. [a] ▪ Refer subject to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. ▪ Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. ▪ If event resolves to Grade 1 or better, resume atezolizumab. [b] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor. [c]
Pulmonary event, Grade 3 or Grade 4	▪ Permanently discontinue atezolizumab and contact the Sponsor. [c] ▪ Bronchoscopy or BAL is recommended. ▪ Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. ▪ If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ▪ If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL=bronchoscopic alveolar lavage; IVIG=intravenous immunoglobulin

a. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor

11.6.2.2 Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible subjects must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment.

While in this study, subjects who present with right upper-quadrant abdominal pain or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

If LFTs worsened, concurrent medications, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

For specific management guidelines please see Table 4.

Table 4. Management Guidelines for Hepatic Events

Adverse Event	Management
Hepatic event, Grade 1	▪ Continue atezolizumab. ▪ Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	All events:

Adverse Event	Management
	▪ Monitor LFTs more frequently until return to baseline values. Events of >5 days' duration: ▪ Withhold atezolizumab for up to 12 weeks after event onset.[a] ▪ Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. ▪ If event resolves to Grade 1 or better, resume atezolizumab.[b] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact
Hepatic event, Grade 3 or 4	▪ Permanently discontinue atezolizumab and contact the Sponsor.[c] ▪ Consider subject referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. ▪ Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. ▪ If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ▪ If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT =liver function tests.

a. Atezolizumab may be withheld for a longer period (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be agreed upon by the investigator and the Sponsor.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor

11.6.2.3 Gastrointestinal Events

Immune-mediated colitis has been associated with the administration of atezolizumab.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. If the event is of significant duration or magnitude or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased C-reactive protein [CRP], platelet count, or bandemia), the following are recommended:

- Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with 3 to 5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates for confirmation of the diagnosis of colitis.

For specific management guidelines please see Table 5.

Table 5. Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Adverse Event	Management
Diarrhea or colitis, Grade 1	▪ Continue atezolizumab. ▪ Initiate symptomatic treatment. ▪ Endoscopy is recommended if symptoms persist for >7 days. ▪ Monitor closely.
Diarrhea or colitis, Grade 2	▪ Withhold atezolizumab for up to 12 weeks after event onset.[a] ▪ Initiate symptomatic treatment. ▪ Subject referral to GI specialist is recommended. ▪ For recurrent events or events that persist >5 days, initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent.

Adverse Event	Management
	▪ If event resolves to Grade 1 or better, resume atezolizumab. [b] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor. [c]
Diarrhea or colitis, Grade 3	▪ Withhold atezolizumab for up to 12 weeks after event onset. [a] ▪ Refer subject to gastrointestinal specialist for evaluation and confirmatory biopsy. ▪ Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ▪ If event resolves to Grade 1 or better, resume atezolizumab. [b] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor [c]
Diarrhea or colitis, Grade 4	▪ Permanently discontinue atezolizumab and contact the Sponsor.[c] ▪ Refer subject to gastrointestinal specialist for evaluation and confirmation biopsy. ▪ Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ▪ If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

a. Atezolizumab may be withheld for a longer period (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be agreed upon by the investigator and the Sponsor.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor

11.6.2.4 Endocrine Events

Thyroid disorders, type 1 diabetes mellitus, adrenal insufficiency, and pituitary disorders have been associated with the administration of atezolizumab.

Subjects with unexplained symptoms such as fatigue, myalgias, impotence, constipation, or mental status changes, should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. Thyroid stimulating hormone (TSH), triiodothyronine 3 (T3), and free thyroxine (T4) levels should be obtained to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels and ACTH stimulation test) and MRI of the brain (with detailed pituitary sections) may help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

For specific management guidelines, please see Table 6.

Table 6. Management Guidelines for Endocrine Events

Adverse Event	Management
Asymptomatic hypothyroidism	▪ Continue atezolizumab. ▪ Initiate treatment with thyroid replacement hormone. ▪ Monitor TSH weekly.
Symptomatic	▪ Withhold atezolizumab. ▪ Initiate treatment with thyroid replacement hormone.

Adverse Event	Management
hypothyroidism	▪ Monitor TSH weekly. ▪ Consider subject referral to endocrinologist. ▪ Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	TSH ≥0.1 mU/L and <0.5 mU/L: ▪ Continue atezolizumab. ▪ Monitor TSH every 4 weeks. TSH <0.1 mU/L: ▪ Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	▪ Withhold atezolizumab. ▪ Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. ▪ Consider subject referral to endocrinologist. ▪ Resume atezolizumab when symptoms are controlled and thyroid function is improving. ▪ Permanently discontinue atezolizumab and contact the Sponsor for life-threatening immune-related hyperthyroidism.[a]
Symptomatic adrenal insufficiency, Grade 2-4	▪ Withhold atezolizumab for up to 12 weeks after event onset. [b] ▪ Refer subject to endocrinologist. ▪ Perform appropriate imaging. ▪ Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ▪ If event resolves to Grade 1 or better, resume atezolizumab. [c] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[a]
Hyperglycemia, Grade 1 or 2	▪ Continue atezolizumab. ▪ Initiate treatment with insulin if needed. ▪ Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	▪ Withhold atezolizumab. ▪ Initiate treatment with insulin. ▪ Monitor for glucose control. ▪ Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis pan-hypopituitarism), Grade 2-3	▪ Withhold atezolizumab for up to 12 weeks after event onset. [b] ▪ Refer subject to endocrinologist. ▪ Perform brain MRI (pituitary protocol). ▪ Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ▪ If event resolves to Grade 1 or better, resume atezolizumab. [c] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[a] ▪ For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis pan-hypopituitarism), Grade 4	▪ Permanently discontinue atezolizumab and contact the Sponsor.[a] ▪ Refer subject to endocrinologist. ▪ Perform brain MRI (pituitary protocol). ▪ Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[b] ▪ Initiate hormone replacement therapy if clinically indicated.

TSH=thyroid-stimulating hormone

a. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the

Adverse Event	Management
immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor. b. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor. c. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed	

11.6.2.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events) referred by the study subjects.

For specific management guidelines, please see Table 7.

Table 7. Management Guidelines for Ocular Events

Adverse Event	Management
Ocular event, Grade 1	▪ Continue atezolizumab. ▪ Subject referral to ophthalmologist is strongly recommended. ▪ Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. ▪ If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	▪ Withhold atezolizumab for up to 12 weeks after event onset.[b] ▪ Subject referral to ophthalmologist is strongly recommended. ▪ Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. ▪ If event resolves to Grade 1 or better, resume atezolizumab.[a] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[c]
Ocular event, Grade 3 or 4	▪ Permanently discontinue atezolizumab and contact the Sponsor.[c] ▪ Refer subject to ophthalmologist. ▪ Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. ▪ If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
a. If corticosteroids have been initiated, they must be tapered over ≥1 month to≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. b. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor. c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor	

11.6.2.6 Immune-Related Myocarditis

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any subject presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a

subject who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy.

All subjects with possible myocarditis should be evaluated urgently by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated. Subjects with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 8.

Table 8. Management Guidelines for Immune-Related Myocarditis

Adverse Event	Management
Immune-related myocarditis, Grade 1	▪ Refer subject to cardiologist ▪ Initiate treatment as per institutional guidelines.
Immune-related myocarditis, Grade 2	▪ Withhold atezolizumab for up to 12 weeks after event onset and contact Sponsor. ▪ Refer subject to cardiologist. ▪ Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. ▪ Consider treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[a] ▪ If event resolves to Grade 1 or better, resume atezolizumab.[b] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[c]
Immune-related myocarditis, Grade 3 or 4	▪ Permanently discontinue atezolizumab and contact Sponsor.[c] ▪ Refer subject to cardiologist ▪ Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. ▪ Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[a,b] ▪ If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ▪ If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device

a. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor

11.6.2.7 Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should

include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. For specific management guidelines please see Table 9.

Table 9. Management Guidelines for Pancreatic Events, Including Pancreatitis

Adverse Event	Management
Amylase and/or lipase elevation, Grade 2	▪ Continue atezolizumab. ▪ Monitor amylase and lipase weekly. ▪ For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	▪ Withhold atezolizumab for up to 12 weeks after event onset.[a] ▪ Refer subject to gastrointestinal specialist. ▪ Monitor amylase and lipase every other day. ▪ If no improvement, consider treatment with 1-2 mg/kg/day oral prednisone or equivalent. ▪ If event resolves to Grade 1 or better, resume atezolizumab.[b] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[c] ▪ For recurrent events, permanently discontinue atezolizumab and contact the Sponsor.[c]
Immune-related pancreatitis, Grade 2 or 3	▪ Withhold atezolizumab for up to 12 weeks after event onset.[a] ▪ Refer subject to gastrointestinal specialist. ▪ Initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ▪ If event resolves to Grade 1 or better, resume atezolizumab.[b] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.[c] ▪ For recurrent events, permanently discontinue atezolizumab and contact the Sponsor.[c]
Immune-related pancreatitis, Grade 4	▪ Permanently discontinue atezolizumab and contact the Sponsor.[c] ▪ Refer subject to gastrointestinal specialist. ▪ Initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ▪ If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ▪ If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

a. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor

11.6.2.8 Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent or severe rash or pruritus. A biopsy should be considered unless contraindicated. For specific management guidelines please see Table 10.

Table 10. Management Guidelines for Dermatologic Events

Adverse Event	Management
Dermatologic event, Grade 1	▪ Continue atezolizumab. ▪ Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	▪ Continue atezolizumab. ▪ Consider subject referral to dermatologist. ▪ Initiate treatment with topical corticosteroids. ▪ Consider treatment with higher-potency topical corticosteroids if event does not improve
Dermatologic event, Grade 3	▪ Withhold atezolizumab for up to 12 weeks after event onset. ▪ Refer subject to dermatologist. ▪ Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. ▪ If event resolves to Grade 1 or better, resume atezolizumab.[b] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor.
Dermatologic event, Grade 4	▪ Permanently discontinue atezolizumab and contact the Sponsor.[c]

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor

11.6.2.9 Neurologic Disorders

Myasthenia gravis, Guillain-Barré syndrome, and meningoencephalitis have been observed with single agent atezolizumab. Subjects may present with signs and symptoms of sensory or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternate etiologies. For specific management guidelines please see Table 11.

Table 11. Management Guidelines for Neurologic Disorders, Including Meningoencephalitis

Adverse Event	Management
Immune-related neuropathy, Grade 1	▪ Continue atezolizumab. ▪ Investigate etiology.
Immune-related neuropathy, Grade 2	▪ Withhold atezolizumab for up to 12 weeks after event onset.[a] ▪ Investigate etiology. ▪ Initiate treatment as per institutional guidelines. ▪ If event resolves to Grade 1 or better, resume atezolizumab.[b] ▪ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the sponsor
Immune-related neuropathy, Grade 3 or 4	▪ Permanently discontinue atezolizumab and contact the Sponsor.[c] ▪ Initiate treatment as per institutional guidelines.

Adverse Event	Management
Myasthenia gravis and Guillain-Barré syndrome (any grade)	▪ Permanently discontinue atezolizumab and contact the Sponsor.[c] ▪ Refer subject to neurologist. ▪ Initiate treatment as per institutional guidelines. ▪ Consider initiation of 1-2 mg/kg/day oral or IV prednisone or equivalent.
Immune-related meningoencephalitis, all grades	▪ Permanently discontinue atezolizumab and contact the Sponsor.[c] ▪ Refer subject to neurologist. ▪ Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ▪ If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ▪ If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

IV=intravenous

a. Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Sponsor

11.6.2.10 Immune-Related Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any subject presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process. All subjects being considered for meningoencephalitis should be evaluated urgently with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted. For specific management guidelines.

11.6.2.11 Immune-related Nephritis

Immune-related nephritis is an identified risk associated with the administration of atezolizumab. Immune-related nephritis is a relatively rare complication of checkpoint inhibitor therapy with the most common reported underlying pathology being acute tubulo-interstitial nephritis (ATIN). The most common presentation is asymptomatic increase in creatinine levels. In the absence of alternative etiologies (e.g., prerenal and postrenal causes, and concomitant medications), immune-related nephritis is defined as renal dysfunction requiring steroids treatment and/or confirmed by biopsy. For specific management guidelines, please see Table 12.

Table 12. Management Guidelines for Immune-Related Nephritis

Adverse Event	Management
Immune-related nephritis, Grade 2	▪ Withhold atezolizumab and contact Sponsor. ▪ Refer subject to renal specialist ▪ Initiate treatment as per institutional guidelines and consider renal biopsy and supportive measures. ▪ Corticosteroids and/or additional immunosuppressive agents should be administered as clinically indicated.
Immune-related nephritis, Grade 3-4	▪ Permanently discontinue atezolizumab and contact Sponsor. ▪ Refer subject to renal specialist ▪ Initiate treatment as per institutional guidelines and consider renal biopsy and supportive measures. ▪ Corticosteroids and/or additional immunosuppressive agents should be administered as clinically indicated.

11.6.2.12 Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for subjects who, in the absence of an alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- Complete blood count (CBC) with peripheral smear
- Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, total bilirubin
- Lactate dehydrogenase (LDH)
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)
- Serum sample for cytokine analysis

If systemic immune activation is still suspected after the initial evaluation, atezolizumab should be withheld with the provision of appropriate supportive medical care, including corticosteroid therapy. The Sponsor should be contacted for additional recommendations. Please see Table 13.

Table 13. Systemic Immune Activation

Systemic Immune Activation	
Major Criteria	Minor Criteria
▪ Fever ≥ 38.5ºC (on more than one occasion) ▪ Ferritin > 3000 ng/mL	▪ Splenomegaly ▪ Hemophagocytosis

Systemic Immune Activation		
Major Criteria		Minor Criteria
▪ Cytopenias Grade 2 in two or more lineages ▪ ≥2 age-adjusted SD elevation soluble IL-2 receptor ▪ Severe multi-organ dysfunction ▪ Decreased fibrinogen		BM, spleen or LN ▪ Elevated GGT or LFTs (AST/ALT/tBili) ▪ Elevated triglycerides ▪ Elevated LDH ▪ Decreased natural killer-cell activity
	Number of Criteria	Management
Consistent with systemic immune activation	4 criteria	Permanently discontinue atezolizumab and contact the Sponsor. Consider referring to an immunologist for evaluation Consider treatment with methylprednisolone, or equivalent, or the best way of treatment according to the physician's judgement.
Probable systemic immune Activation	3 major criteria OR 2 major criteria AND 3 minor criteria	Depending on clinical severity, subject can be treated as per "Consistent with systemic immune activation" or "Possible systemic immune activation" case definition. Contact the Sponsor for additional recommendations
Possible systemic immune Activation	1 major criteria	Consider methylprednisolone (1g IV QD) Contact the Sponsor for additional recommendations. As per "Consistent with systemic immune activation" recommendations if no improvement or clinically worsening
BM = bone marrow; GGT = gamma-glutamyl transpeptidase; IL-2 = interleukin-2; IV = intravenous; LFT = liver function test; LN= lymph node; QD = once daily; tBili = total bilirubin. Notes: Criteria adapted from a Delphi Survey of 26 experts regarding helpful criteria in the positive diagnosis of Hemophagocytic Syndrome in adult subjects (Hejblum G. et al PLoS One, April 2014; Volume 9, Issue 4). Standard-of-care for systemic immune activation has not been established. Case reports and recommendations have been published for cytokine release syndrome (*Lee 2014*, *Maude 2014*, *Teachey 2013*), and based on etiologic similarities, these practices have been incorporated into the above treatment recommendations. These recommendations do not replace clinical judgment and are intended as suggested guidance.		

11.6.2.13 Infusion-related Reactions

No premedication is indicated for the administration of atezolizumab in Cycle 2. Subjects who experience an infusion-related reaction (IRR) with Cycle 2 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab associated IRRs, due to its potential for causing agranulocytosis. Table 14 provides management guidelines for atezolizumab IRRs in Cycle 2.

Severity	**Management**
Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate.

Severity	Management
	• If tolerated, the infusion rate may then be increased to the original rate
Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Restart only after the symptoms have adequately resolved to baseline grade. • The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR. • At next cycle, administer oral premedication with antihistamine and anti-pyretic and monitor closely for IRR.
Grade 3-4	• Stop infusion. • Proper medical management which may include oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen • Discontinue atezolizumab. • Contact the Sponsor if atezolizumab is discontinued.
IRR = infusion-related reaction; IV = intravenous.	

For subsequent cycles, infusion-related reactions should be managed according to institutional guidelines.

11.7 Disposition of Used Supplies

The blisters, cartons or bottles either used by the subjects or unused, must not be destroyed until the monitor has verified the accountability of the IMP.

During the trial, at the pre-defined visits, and at termination, patients must return all used and unused study drug supplies, and the return of these unused study drug supplies must be recorded. Returned supplies must not be re-dispensed.

All unused vials or capsules of study drug must be destroyed in an appropriate manner according to the standard practice at each study center. Destruction of such supplies will be documented, and a representative of the sponsor will verify disposition records.

No other utilization of the bosutinib and atezolizumab intended for use in this study is authorized by the Sponsor. The principal investigator or his/her designee will be responsible for the appropriate handling and disposition of residual study drugs. Each site is responsible for proper and careful destruction of study drug returned by patients.

11.8 Inventory of Unused Supplies

Periodically throughout the study and at its conclusion, a representative of the sponsor will conduct an inventory of unused study drugs. At the completion of the trial, a final study drug accountability review will be conducted. Any discrepancies must be investigated. All unused study drug must be destroyed on site following the standard operating procedures of the investigative site.

12 VISIT SCHEDULE AND ASSESSMENTS

12.1 Schedule of Events

Details on scheduling and sample collection are described in Tables 14-17. The tables 14 and 15 for 1st group of patients (first 10 patients included), and the tables 16 and 17 for 2nd group of patients (the last 26 patients included).

All data obtained from these assessments must be recorded in the source documentation. The CRF will not be used as a source document for any study data.

Please maintain a special awareness of the assessments of the primary and secondary endpoints.

All visits should be completed on the designated day or as close as possible. However, the windows allowed by protocol will be:

- For visits that take place every two weeks, the window will be ±3 days.
- For visits that take place every 4 weeks, the window will be ±3 days.
- For visits that take place every 3 cycles (every 12 weeks), and the End of Treatment visit, the window allowed will be ±14 days.

For this purpose, a cycle equal to 28 days (4 weeks) will be defined and one month will be considered to be equivalent to one cycle.

Table 14. Schedule of Assessments 1st and 2nd Therapies for the First 10 Patients

The following visit schedule will apply if the atezolizumab dose does not need to be adjusted during 2nd therapy due to DLTs. If the dose of atezolizumab has to be modified to the 840 mg every two weeks, additional visits will be scheduled for the administration of atezolizumab. The only procedure to be conducted during these additional visits is the administration of atezolizumab

1st Group of Patients (The 10 First Patients)		**1st Therapy**		**2nd Therapy**													
VISIT	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**
Cycle	**Screening / Baseline**	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycle 8**	**Cycle 9**	**Cycle 10**	**Cycle 11**	**Cycle 12**	**Cycle 13**
Day within Cycle (Visit Window ± 3 Days)	**-28/-1**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Consecutive Days in the Study (D)	**-28/-1**	**D1**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D113**	**D141**	**D169**	**D197**	**D225**	**D253**	**D281**	**D309**	**D337**
Informed Consent	**X**																
Eligibility	**X**	**X(1)**															
Inclusion/Exclusion Criteria (Checklist)	**X**	**X(1)**															
Medical/Surgical History and Demographics	**X**																
Recent Medication Prior to First Dose of IMP	**X**	**X(1)**															
Leukemia Diagnosis and Prior Cancer Therapy	**X**																
Sokal Risk Score	**X**																
Vital Signs	**X**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**	**X(1)**
Weight	**X**	**X(1)**		**X(1)**				**X(1)**			**X(1)**			**X(1)**			**X(1)**
Height	**X**																
12-Lead Electrocardiogram	**X**			**X(1)**	**As clinically indicated**												
Physical Examination and Extra-medullary Leukemia Involvement	**X**	**X(1)**	**X(1)**	**X(1)**				**X(1)**			**X(1)**			**X(1)**			**X(1)**
ECOG	**X**	**X(1)**		**X(1)**				**X(1)**			**X(1)**			**X(1)**			**X(1)**
Blood Sample for BCR-ABL1 Assessment	**X**			**X(1)**				**X(1)**			**X(1)**			**X(1)**			**X(1)**

1st Group of Patients (The 10 First Patients)		1st Therapy		2nd Therapy													
VISIT	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**
Cycle	**Screening / Baseline**	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycle 8**	**Cycle 9**	**Cycle 10**	**Cycle 11**	**Cycle 12**	**Cycle 13**
Day within Cycle (Visit Window ± 3 Days)	**-28/-1**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Consecutive Days in the Study (D)	**-28/-1**	**D1**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D113**	**D141**	**D169**	**D197**	**D225**	**D253**	**D281**	**D309**	**D337**
Complete Blood Count with Differential	**X**	**X(1)**	**X(1)**	**X(1)**				**X(1)**			**X(1)**			**X(1)**			**X(1)**
Chemistry	**X(2)**	**X(1)**		**X(1)(2)**				**X(1)(2)**			**X(1)(2)**			**X(1)(2)**			**X(1)(2)**
Serology	**X**																
Bone Marrow Aspirate and Cytogenetic, if no-CCyR	**X**							**X**			**X**			**X**			**X**
Pregnancy Test		**X**		**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Immunological Studies	**X**			**X(1)**													**X(1)**
Adverse Events	**Medical History**	**Continuous**															
Concomitant Medications	**Medical History**	**Continuous**															
Dispensing or Return of **Bosutinib**		**X(4)**						**X**			**X**			**X**			**X**
Atezolizumab Administration				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

(1): The tests will be performed before IMP dose administration.
(2): Determination of lipase and amylase levels included.
(3): If the patient achieves CCYR, the cytogenetic assessment is not necessary.
(4) Dispense only bousutinib treatment.

Table 15. Schedule of Assessments 3rd Therapy for the first 10 patients

1st Group of Patients	3rd Therapy					
VISIT	**Visit 17**	**Visit 18**	**Visit 19**	**Visit 20**	**Visit 21 (EOT)**	**Visit 22 (EOS)**
Cycle	**Cycle 14**	**Cycle 17**	**Cycle 20**	**Cycle 23**	**Cycle 25**	**Follow-up**
Day within Cycle (Visit Window ± 14 Days)	**1**	**1**	**1**	**1**	**29**	**28 days after the last dose**
Consecutive Days in the Study (D)	**D365**	**D449**	**D533**	**D617**	**D700**	**D728**
Vital Signs	**X(1)**	**X**	**X**	**X**	**X**	**X**
Weight	**X(1)**	**X**	**X**	**X**	**X**	**X**
12-Lead Electrocardiogram	**As clinically indicated**					**X**
Physical Examination and Extra-Medullary Leukemia Involvement	**X(1)**	**X**	**X**	**X**	**X**	**X**
ECOG	**X(1)**	**X**	**X**	**X**	**X**	**X**
Blood Sample for BCR-ABL1 Assessment		**X**	**X**	**X**	**X**	
Complete Blood Count with Differential	**X(1)**	**X**	**X**	**X**	**X**	**X**
Chemistry	**X(1)**		**X**		**X**	**X**
Bone Marrow Aspirate and Cytogenetic, if No CCYR	**X**	**X**	**X**	**X**	**X**	**X**
(2)Pregnancy Test	**X**	**X**	**X**	**X**	**X**	**X**
Immunological Studies	**X(1)**				**X**	**X**
Adverse Events	**Continuous**					
Concomitant Medications	**Continuous**					
Dispensing or Return of **Bosutinib**	**X**	**X**	**X**	**X**	**X (Return)**	

(1): The tests will be performed before bosutinib administration
(2): Between visits to the center, the patient will perform a pregnancy test each month at her house.

Table 16: Schedule of Assessments 3rd Phase for Other 26 Patients

2nd Group of patients (The Next 26 Patients)		1st Therapy		2nd Therapy											
VISIT	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**
Cycle	**Screening / Baseline**	**Cycle 1**		**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycle 8**	**Cycle 9**	**Cycle 10**	**Cycle 11**	**Cycle 12**	**Cycle 13**
Day within Cycle (Visit Window ± 3 Days)	**-28/-1**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Consecutive Days in the Study (D)	**-28/-1**	**D1**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D197**	**D225**	**D253**	**D281**	**D309**	**D337**
Informed Consent	X														
Eligibility	X	X(1)													
Inclusion/Exclusion Criteria (Checklist)	X	X(1)													
Medical/Surgical History and Demographics	X														
Recent Medication Prior to First Dose of IMP	X	X(1)													
Leukemia Diagnosis and Prior Cancer Therapy	X														
Sokal Risk Score	X														
Vital Signs	X	X(1)	X(1)	X(1)	X(1)	X(1)	X(1)	X(1)	X(1)	X(1)	X(1)	X(1)	X(1)	X(1)	X(1)
Weight	X	X(1)		X(1)		X(1)			X(1)			X(1)			X(1)
Height	X	**As clinically indicated**													
12-Lead Electrocardiogram	X			X(1)	**As clinically indicated**										
Physical Examination and Extra-medullary Leukemia Involvement	X	X(1)	X(1)	X(1)		X(1)			X(1)			X(1)			X(1)
ECOG	X	X(1)		X(1)		X(1)			X(1)			X(1)			X(1)
Blood Sample for BCR-ABL1 Assessment	X			X(1)		X(1)			X(1)			X(1)			X(1)
Complete Blood Count with Differential	X	X(1)	X	X(1)		X(1)			X(1)			X(1)			X(1)
Chemistry	X(2)	X(1)		X(1)(2)		X(1)(2)			X(1)(2)			X(1)(2)			X(1)(2)

2nd Group of patients (The Next 26 Patients)		1st Therapy		2nd Therapy											
VISIT	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**
Cycle	**Screening / Baseline**	**Cycle 1**		**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycle 8**	**Cycle 9**	**Cycle 10**	**Cycle 11**	**Cycle 12**	**Cycle 13**
Day within Cycle (Visit Window ± 3 Days)	**-28/-1**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Consecutive Days in the Study (D)	**-28/-1**	**D1**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D197**	**D225**	**D253**	**D281**	**D309**	**D337**
Serology	**X**														
Bone Marrow Aspirate and Cytogenetic, if no-CCyR	**X**					**X**			**X**			**X**			**X**
Pregnancy Test		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Immunological Studies	**X**			**X**(1)											**X**(1)
Adverse Events	**Medical History**	**Continuous**													
Concomitant Medications	**Medical History**	**Continuous**													
Dispensing or Return of **Bosutinib**		**X**(4)				**X**			**X**			**X**			**X**
Atezolizumab Administration				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

(1): The tests will be performed before IMP dose administration.
(2): Determination of lipase and amylase levels included.
(3): If the patient achieves CCYR, the cytogenetic assessment is not necessary.
(4) Dispense only bousutinib treatment.

Table 17. Schedule of assessments 3rd Therapy for Other 26 patients

2nd Group of Patients	3rd Therapy					
VISIT	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19 (EOT)**	**Visit 20 (EOS)**
Cycle	**Cycle 14**	**Cycle 17**	**Cycle 20**	**Cycle 23**	**Cycle 25**	**Follow-up**
Day within Cycle (Visit Window ± 14 Days)	**1**	**1**	**1**	**1**	**29**	**28 days after the last dose**
Consecutive Days in the Study (D)	**D365**	**D449**	**D533**	**D617**	**D700**	**D728**
Vital Signs	**X(1)**	**X**	**X**	**X**	**X**	**X**
Weight	**X(1)**	**X**	**X**	**X**	**X**	**X**
12-Lead Electrocardiogram	**As clinically indicated**					**X**
Physical Examination and Extra-Medullary Leukemia Involvement	**X(1)**	**X**	**X**	**X**	**X**	**X**
ECOG	**X(1)**	**X**	**X**	**X**	**X**	**X**
Blood Sample for BCR-ABL1 Assessment		**X**	**X**	**X**	**X**	
Complete Blood Count with Differential	**X(1)**	**X**	**X**	**X**	**X**	**X**
Chemistry	**X(1)**		**X**		**X**	**X**
Bone Marrow Aspirate and Cytogenetic, if No CCYR	**X**	**X**	**X**	**X**	**X**	**X**
(2)Pregnancy Test	**X**	**X**	**X**	**X**	**X**	**X**
Immunological Studies	**X(1)**				**X**	**X**
Adverse Events	**Continuous**					
Concomitant Medications	**Continuous**					
Dispensing or Return of **Bosutinib**	**X**	**X**	**X**	**X**	**X (Return)**	

(1): The tests will be performed before bosutinib administration.
(2): Between visits to center, the patient will perform a pregnancy test at her house.

The following describes the procedures/tests required for this study:

12.2 Screening Period Procedures

Written informed consent must be obtained before performing any study specific medical procedures. The screening visit will take place at study days -28 to zero. All patients must take part in the informed consent process. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. Adequate time must be allowed for the patient to make questions and to make a voluntary decision. No protocol-specific procedures are to be performed until the patient has signed and dated an informed consent form (IC) approved by an Ethics Committee for investigation with medicinal products (CEIm). Each patient's participation in the trial begins with the signing and dating of the informed consent form.

During the screening visit, inclusion and exclusion criteria will be assessed.

For details of assessments required during screening, please refer to Tables 14 and 16.

The screening RT-qPCR blood sample will be analyzed by a Sponsor designated central laboratory. In case the BCR-ABL1 status cannot be determined on this sample (e.g., due to technical or logistical issues) another blood sample for RT-qPCR is to be collected immediately and submitted to the central laboratory for determination of the BCR-ABL1 status.

Laboratory baseline assessments (including hematology and chemistry), physical examination including performance status, height, weight, ECG and vital signs must be performed within 28 days prior to Cycle 1/study Day 1, before the first IMP dose. As long as a patient that has signed the IC fulfill all inclusion criteria and none of the exclusion criteria, he/she could be included in this study.

12.3 Eligibility Screening

The investigator will send the eligibility check form to the Sponsor by email (farmacovigilancia@ifth.es). The investigator will be allowed to assign treatment to the patient if he/she fulfills all inclusion criteria and none exclusion criteria.

12.4 Information to Be Collected on Screening Failures

Patients who sign the study informed consent but fail to start the treatment for any reason will be considered a screen failure. The reason(s) for not starting the treatment will be recorded on the source document and the CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screening Failure patients, if it is possible. No other data will be entered into the CRF for those subjects who are screen failures.

12.5 Medical/Surgical History and Demographics

Medical and surgical history and demographic information will be recorded. Medical and surgical history includes diagnoses, therapies, and medical and surgical treatments.

Demographic information consists of the patient's age, gender, and race.

12.6 Recent Medication Prior to First IMP Dose

The relevant medication at the time of the IC signature will be obtained from each patient at the time of screening and before the first IMP dose. It will be recorded in the CRF.

12.7 Leukemia Diagnosis and Prior Cancer Therapy

Both the initial leukemia diagnosis and the current screening diagnosis must be recorded. Note: Only patients currently in CP-CLM and those with no prior history of CML-AP, or CML-BC, or stem cell transplant are eligible.

12.8 Sokal Risk Score

Sokal risk score will be collected at screening. Risk category based on Sokal score is calculated using the following formula based on parameters from time of diagnosis:

Table 18: Sokal Formulation

Sokal Variables (from Sokal *et al*, 1984)	
Age (years) * Spleen (cm) Platelets (x 10^9/L) ^ Blasts (%)	0.0116 (age - 43.4) 0.0345 (spleen - 7.51) 0.188 [(platelets/700)^2 – 0.563] 0.0887 (blasts - 2.10)
Relative Risk (RR)	Exponential of the total
* Maximum distance from costal region ^ Percent in peripheral blood	

In the Sokal formulation, all four variables are continuous.

- Low risk patients have a Relative Risk (RR) < 0.8
- Intermediate risk patients have a RR ≥ 0.8 and ≤ 1.2
- High risk patients have a RR > 1.2

12.9 Vital Signs

Vital signs are temperature, pulse, respiratory rate, and blood pressure (when the patient is seated). The vital signs must be performed before treatment at the following visits:

- Screening
- During first therapy:
    - Day 1 of cycle 1 (before treatment).
    - Day 15 of cycle 1
- During second therapy (before treatment):

- Day 1 of cycle 2. Before the patient takes the bosutinib plus atezolizumab combination for first time.
- The vital signs test should also be performed on days 15 of cycles 2 and 3, only for the first group of patients.
- Day 1 of cycles 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13.

- During third therapy:
  - Day 1 of cycle 14. Before the patient takes bosutinib 400 mg/day in monotherapy, for the first time again for the treatment of CML.
  - Day 1 of cycles 17, 20 and 23.
  - At the End of Treatment: Day 29 (Last dose) of cycle 25.
  - At the End of Study, (visit EOS or follow up): 28 days after the last dose.

12.10 Height and Weight

Height in centimeters (cm) and body weight in Kg (reported to the first decimal) (in indoor clothing, but without shoes) will be measured.

Height measurement is required at screening only.

Weight will be measured at:

- Screening
- During first therapy (before treatment):
  - Day 1 of cycle 1.
- During second therapy (before treatment):
  - Day 1 of cycle 2. Before the patient takes the bosutinib plus atezolizumab combination for first time.
  - Day 1 of cycles 4, 7, 10, and 13.
- During third therapy:
  - Day 1 of cycle 14. Before the patient takes bosutinib 400 mg/day in monotherapy, for the first time again for the treatment of CML.
  - Day 1 of cycles 17, 20 and 23.
  - At the End of Treatment: Day 29 (Last dose) of cycle 25.
  - At the End of Study, (visit EOS or follow up): 28 days after the last dose.

12.11 Electrocardiogram

The screening ECG must be performed within the 28-day screening, also during the first visit of the 2nd cycle, before starting the treatment with Atezolizumab, and during the EoS visit in all participants. If medications known to prolong the QTcF interval are used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated.

12.12 Physical Examination and Extra-medullary Leukemia Involvement

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. Presence of extra-medullary leukemic involvement will be checked along with each physical examination as outlined above. Findings on physical examination consistent with extra-medullary leukemic involvement will be recorded (e.g., lymph nodes, liver and spleen size). With regards to lymph nodes, only those palpable lymph nodes should be considered to be CML related if leukemic blast infiltration has been confirmed via biopsy/histology or by technically adequate (not contaminated with peripheral blood) aspiration cytology. When extra-medullary involvement other than the spleen or liver is the only evidence of blast crisis, this finding must be confirmed by technically adequate (not contaminated with peripheral blood) aspiration cytology and /or biopsy (especially for isolated lymph nodes) and data entered into the extra-medullary involvement eCRF.

Information about the physical examination must be present in the source documentation at the study center and will be collected during the following visits:

- Screening
- During first therapy:
  - Day 1 of cycle 1 (before treatment).
  - Day 15 of cycle 1.
- During second therapy (before treatment):
  - Day 1 of cycle 2. Before the patient takes the bosutinib plus atezolizumab combination for first time.
  - Day 1 of cycles 4, 7, 10, and 13.
- During third therapy:
  - Day 1 of cycle 14. Before the patient takes bosutinib 400 mg/day in monotherapy, for the first time again for the treatment of CML.
  - Day 1 of cycles 17, 20 and 23.
  - At the End of Treatment: Day 29 (Last dose) of cycle 25.
  - At the End of Study, (visit EOS or follow up): 28 days after the last dose.

12.13 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status should be evaluated during each physical examination.

Table 19. ECOG Performance Status Scale

Description	Grade
Fully active, able to carry on all pre-disease activities without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, office work.	1

Description	Grade
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead.	5

Information about ECOG must be recorded in the source documentation at the study center and will be collected on the following visits:

- Screening
- During first therapy (before treatment):
  - Day 1 of cycle 1 (visit 1/D1).
- During second therapy (before treatment):
  - Day 1 of cycle 2. Before the patient takes the bosutinib plus atezolizumab combination for first time.
  - Day 1 of cycles 4, 7, 10, and 13.
- During third therapy:
  - Day 1 of cycle 14. Before the patient takes bosutinib 400 mg/day in monotherapy, for the first time again for the treatment of CML.
  - Day 1 of cycles 17, 20 and 23.
  - At the End of Treatment: Day 29 (Last dose) of cycle 25.
  - At the End of Study, (visit EOS or follow up): 28 days after the last dose.

12.14 Blood Samples for BCR-ABL Molecular Response Assessment

MR will be assessed in all patients. Levels of BCR-ABL transcripts will be determined by real-time quantitative PCR (RT-qPCR) testing of peripheral blood and analyzed at a FTH designated central laboratory. The percent ratio of BCR-ABL transcripts versus control gene transcripts converted to IS will be calculated for each sample.

RT-qPCR will be done on:

- Screening
- During second therapy (before treatment):
  - Day 1 of cycle 2. Before the patient takes the bosutinib plus atezolizumab combination for first time.
  - Day 1 of cycles 4, 7, 10, and 13.
- During third therapy:
  - Day 1 of cycles 17, 20 and 23.
  - At the End of Treatment: Day 29 (Last dose) of cycle 25.

12.15 Laboratory Evaluations

Local laboratories will be used for analysis of hematology specimens collected and for analysis of biochemistry and serology specimens collected.

12.15.1 Complete Blood Count (CBC) With Differential

CBC with differential is defined as peripheral blood total white blood cell (WBC) count, hemoglobin, hematocrit, platelet count, red blood cell count, leucocytes, absolute neutrophil count (ANC), and WBC differential, reported individually for each cell type. Hematologic assessments must be obtained at:

- Screening
- During first therapy:
  - Day 1 of cycle 1 (before treatment).
  - Day 15 of cycle 1.
- During second therapy (before treatment):
  - Day 1 of cycle 2. Before the patient takes the bosutinib plus atezolizumab combination for first time.
  - Day 1 of cycles 4, 7, 10, and 13.
- During third therapy:
  - Day 1 of cycle 14. Before the patient takes bosutinib 400 mg/day in monotherapy, for the first time again for the treatment of CML.
  - Day 1 of cycles 17, 20 and 23.
  - At the End of Treatment: Day 29 (Last dose) of cycle 25.
  - At the End of Study, (visit EOS or follow up): 28 days after the last dose.

12.15.2 Chemistry

Serum chemistry consists of a peripheral blood draw with the following assessments: sodium, potassium, blood urea nitrogen (BUN) or urea, fasting glucose, albumin, creatinine, total cholesterol, triglycerides, total bilirubin (direct and indirect, only if total bilirubin is out normal range), GOT, GPT, GGT, alkaline phosphatase, LDH, magnesium, phosphorous and calcium. Amylase and lipase determinations will be added only in screening and during bosutinib plus atezolizumab combination treatment.

The chemistry assessments must be obtained at:

- Screening
- During first therapy (before treatment):
  - Day 1 of cycle 1 (visit 1/D1).
- During second therapy (before treatment):
  - Day 1 of cycle 2. Before the patient takes the bosutinib plus atezolizumab combination for first time.
  - Day 1 of cycles 4, 7, 10, and 13.

- During third therapy:
  - Day 1 of cycle 14. Before the patient takes bosutinib 400 mg/day in monotherapy, for the first time again for the treatment of CML.
  - Day 1 of cycle 20.
  - At the End of Treatment: Day 29 (Last dose) of cycle 25.
  - At the End of Study, (visit EOS or follow up): 28 days after the last dose.

12.15.3 Serology

At the time of screening, blood serum must be tested for Hepatitis B serology (Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis B surface antibody) hepatitis C and HIV, in all patients.

12.16 Bone Marrow Analysis and Cytogenetics

Bone marrow aspiration will be performed at screening and every three months until Complete Cytogenetic Response (CCyR) is reached or after suspected disease progression.

Cytogenetic response will be assessed as the percentage of Ph+ metaphases in the bone marrow and is defined as the following (a review of a minimum of 20 metaphases is convenient):

- Complete (CCyR) 0% Ph+ metaphases
- Partial (PCyR) - >0 to 35% Ph+ metaphases
- Minor (mCyR) - >35 to 65% Ph+ metaphases
- Minimal - >65 to 95% Ph+ metaphases
- None - >95 to 100% Ph+ metaphases

These exams will be performed and analyzed locally. Quantification of the percentage of Ph+ chromosome metaphases, number of metaphases, number of positive for Ph chromosome, additional chromosomal abnormalities, if applicable, will be collected.

Fluorescent In-situ hybridization (FISH) analysis will not be accepted. If the sample cannot be quantified, the extraction must be repeated as soon as possible.

12.17 Pregnancy Test

The pregnancy test must be a beta-human chorionic gonadotropin (β-HCG) test, using either urine or serum. Women who are not of childbearing potential (status post- hysterectomy, status post-bilateral oophorectomy, or postmenopausal [defined as amenorrhea for at least 12 months]) do not need to have the test performed. If the test is deemed necessary, it must be performed in screening visit or during visit 1 before the first dose of study drug and known to be negative prior to drug administration. Women of childbearing potential at study start must also complete the pregnancy test each month during the study, at the end-of-treatment visit and at the end-of-study visit.

12.18 Inmunological Studies

Samples: whole blood (30 ml in EDTA tubes) from all patients treated with bosutinib.

Maximum number of samples per patient: 6 (180 ml of blood in total in two years).

Blood samples for exploratory imunological and virological analysis will be measured at:

- Screening
- During second therapy (before treatment):
  - Day 1 of cycle 2. Before the patient takes the bosutinib plus atezolizumab combination for first time.
  - Day 1 of cycle 13.
- During third therapy:
  - Day 1 of cycle 14. Before the patient takes bosutinib 400 mg/day in monotherapy, for the first time again for the treatment of CML.
  - At the End of Treatment: Day 29 (Last dose) of cycle 25.
  - At the End of Study, (visit EOS or follow up): 28 days after the last dose.

12.19 Adverse Events and Concomitant Medications

AEs and concomitant medications will be recorded continuously throughout the study, starting on the date of the first administration of the study medication, and, at least, up to the 28-day follow-up visit after the last dose of treatment. New and updated AEs and concomitant medications will be reported within the treatment period; ongoing AEs thought to be at least possibly study-drug related; and all ongoing SAEs should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE, v5.0 grade ≤ 1), stabilize, or are considered to be chronic/irreversible (see section 13 Adverse Events reporting, for more information). Those relevant events that start before the first administration of the study drug will be recorded in the clinical history of the subject.

A maximum discontinuation of 1 month is allowed for the treatment with bosutinib if required due to the onset of adverse events, investigator decision, of other major circumstances. If a subject discontinued treatment for more than one month he/she will be withdrawn from the study and the appropriate follow-up procedures will be conducted. Regarding atezolizumab treatment, fail to administrate up to 3 out of the 11 administrations scheduled will be allowed for a patient to continue in the study. If, for some reasons, atezolizumab could not be administered 4 or more times, during the course of the study, the subject will be withdrawn from the study and the appropriate follow-up procedures will be conducted. All deviations from the scheduled treatments regime shall be recorded in the patients' clinical history and the eCRF and explained if required.

12.20 End of Treatment or Early Termination Procedures

The end of treatment for the early termination visit should be performed within 2 weeks (14 days) of the patient's last dose of study drug or the patient/investigator decision to discontinue treatment. Survival information, stem cell transplantation, TKI therapy status, as well as information on the status of the patient's disease (i.e., disease progression to AP/BC according to protocol definition, or CML related death) will be collected, if applicable. The information may be collected from tests that were performed for the study or as part of the patient's routine medical care.

Patients that finished the study as per protocol will continue to receive treatment for CML, according to standard clinical practice. For those patients who withdraw before the end of the study, their physician will decide the best course of treatment indicated, following the standard clinical practice and current guidelines for the treatment of CML.

12.21 End of Study. Follow-up Safety Procedures

All AEs ongoing or starting within 28 days after end of treatment must be recorded in the eCRF. After this time, ongoing AEs thought to be at least possibly study-drug related, as well as all ongoing SAEs, should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE, v5.0 grade ≤ 1), stabilize, or are considered to be chronic/irreversible.

12.22 Biological Samples Treatment after the End of the Study

During the clinical trial, the management of biological samples will be carried out in accordance with the following:

The blood samples for the evaluation of the BCR-ABL transcript will be analyzed by the molecular biology hematology laboratory of the Doce de Octubre University Hospital, which since 2009 has the UNE-EN ISO9001: 2008 certification and since 2017: accredited by the UNE standard -EN ISO 15189: 2013, complying with all security and confidentiality regulations.

The samples for the immunological study will be analyzed by the AIDS Immunopathology Unit of the National Center for Microbiology, complying with all safety and confidentiality regulations.

The samples will be shipped the same day of the extraction to the corresponding central laboratories; they will not be stored in the centers. The samples will be used exclusively for the analysis foreseen in the protocol, and the surpluses will be destroyed after its completion.

The provisions of Law 14/2007, of July 3, on Biomedical Research and Royal Decree 1716/2011, of November 18, which establishes the basic requirements for authorization and operation of Biobanks with Biomedical research purposes and the

treatment of biological samples of human origin, and the operation and organization of the National Registry of Biobanks for biomedical research is regulated.

13 ADVERSE EFFECTS REPORTING

13.1 AE Definition

An AE is any untoward medical occurrence in a trial subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding),symptom, or disease temporally associated with the use of a medicinal product, whether or not that sign, symptom, or disease is considered related to the medicinal product. Adverse event is any worsening of a pre-existing condition that is temporally associated or not with the use of the study drug.

The adverse events that occurs since the patient signs the ICF but before he/she takes the first bosutinib dose will be considered as part of the clinical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
AEs include:

- Clinically significant abnormal test findings
- Clinically significant changes in physical exam findings
- Other untoward medical events, regardless of their relationship to the study drug, such as injury, events that require surgery, accidents, or apparently unrelated illnesses
- Hypersensitivity

Additionally, AEs may include signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency
- Product complaint

13.2 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms that are considered clinically significant in the opinion of the investigator.
- Test result requires additional diagnostic testing (other than merely repeating an abnormal test) or medical/surgical intervention.
- Test result leads to a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Test result is considered to be clinically significant by the investigator or sponsor.

13.3 Performing AE Assessment

All observed AEs, regardless of suspected causal relationship to the investigational product, will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to FTH or its designated representative.

13.4 Reporting Period

The investigator shall report all SAEs and AESIs to FTH (farmacovigiliancia@ifth.es) and Pfizer without undue delay but not later than 24 hours from the time he/she has knowledge of these events. The investigator, where applicable, shall send a follow-up report to the sponsor to allow the sponsor to assess whether the serious adverse event has impact on the benefit-risk balance of the clinical trial. The initial and follow-up reports shall identify the trial subjects only by a subject identification code assigned in the trial, specific for each of them.

For all screened patients, beginning at the time of the signature of the informed consent form and concluding 28 days after the last dose of the assigned study treatment or the investigator/patient decision to discontinue treatment or end of study (whichever occurs later), n-TEAEs, and AEs (both serious and non-serious) should be recorded on the eCRF.

Adverse event monitoring should start when the patient takes the study treatment for first time, and continued for at least 28 days following the last dose of study treatment or the investigator/patient decision to discontinue treatment (whichever occurs later).

AEs Ongoing after the Reporting Period: Any ongoing AE should be followed at least every 4 weeks, until they resolve to baseline, stabilize, or are considered to be chronic/irreversible.

SAEs starting after End of Study: SAEs occurring to a patient after the participation of that patient has ended should be reported to the sponsor if the investigator becomes aware of them. The investigator does not need to actively monitor subjects for AEs once the trial has ended.

13.5 AE Severity

The severity of AEs will be assessed according to the NCI CTCAE, v5.0 (see Appendix C and the study Reference Manual). If the AE is not defined in the CTCAE, the investigator will determine its severity based on the following definitions:

- *Mild (grade 1):* The AE is noticeable to the patient but does not interfere with routine activity.
- *Moderate (grade 2):* The AE interferes with routine activity but responds to symptomatic therapy.
- *Severe (grade 3):* The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.
- *Life-threatening (grade 4):* The patient is at immediate risk of death.
- *Death (grade 5):* The patient dies as a direct result of the complication or condition induced by the AE.

13.6 Causality

The investigator's assessment of causality must be provided for all AEs (serious and non-serious). An investigator's causality assessment is the determination of whether there is a reasonable possibility that the investigational product caused or contributed to the AE.

In addition, if the investigator determines that a SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and on the SAE form. The investigator must report such assessment in accordance with the SAE reporting requirements.

The investigator will use both medical consideration and the following categories of causality to determine the causal relationship of an AE to the study drug (based on the definitions below). Not all criteria in each category of relatedness must be present.

Definitely Not Related (Not Drug-Related)

- The patient did not receive study drug, or
- The temporal sequence of the AE onset, relative to the administration of study drug, is not reasonable, or
- There is another obvious cause for the AE

Probably Not Related (Not Drug-Related)

There is evidence of exposure to study drug and one of the following:

- There is another, more likely cause of the AE
- Dechallenge (if performed) is negative or ambiguous
- Rechallenge (if performed) is negative or ambiguous

Possibly Related (Drug-Related)

There is evidence of exposure to study drug and one of the following:

- The temporal sequence of the AE onset, relative to administration of study drug, is reasonable
- The AE could have been due to another equally likely cause
- Dechallenge (if performed) is positive

Probably Related (Drug-Related)

There is evidence of exposure to study drug and one of the following:

- The temporal sequence of the AE onset, relative to administration of study drug, is reasonable
- The AE is more likely explained by study drug than by another cause

Definitely Related (Drug Related)

There is evidence of exposure to study drug and one of the following:

- The temporal sequence of the AE onset, relative to administration of study drug, is reasonable
- Dechallenge is positive
- The AE shows a pattern consistent with previous knowledge of the test drug or a test drug class

13.7 Expectedness

The current Clinical Investigator's Brochures (CIB) will be used as the reference for determination of expectedness and risk assessment for bosutinib and atezolizumab.

13.8 SAEs

The definitions and reporting requirements of ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A, as well as the Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry will be followed.

The investigator or sponsor may determine the seriousness of an AE based on the following. An AE is considered a SAE if at least one of these conditions applies:

- *Death:* if the death occurs within the time of the first dose and the 28 days after the last dose and the cause of death is the event.
- *Life-threatening:* An AE that places the patient, in the view of the investigator or the sponsor, at immediate risk of death from the event as it occurred (e.g., this does not include an event that, had it occurred in a more severe form, might have caused death)
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- *Inpatient hospitalization or prolongation of existing hospitalization:* Hospitalization refers to admission of a patient into a hospital for any length of time.
- *A congenital anomaly/birth defect:* A fixed, permanent impairment established at or before birth

- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as serious adverse events SAES.

13.9 Adverse Event of Special Interest (AESI) Definition

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not result in death, be life-threatening, or require hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes listed in the definition above, that important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

13.9.1 Adverse Event of Special Interest

AESIs require ongoing monitoring by investigators and rapid identification and communication by the investigator to the sponsor. All AESIs, whether they are SAEs or not, must be reported immediately (within 24 hours) to the sponsor. The sponsor has determined that the events listed below (whether considered serious or non-serious by investigators) should be considered AESIs, and should therefore be reported within 24 hours:

1) In relation to bosutinib:
   A. Grade 3-4 diarrhea
   B. Grade 3-4 nausea and vomiting
   C. Potential drug-induced liver injury showed by abnormal values in liver enzyme (ALT increased and AST increased) concurrent with abnormal elevation in total bilirubin that meet the criteria outlined below:
      a. Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥3 times the upper limit of normal concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available;
      b. For patients with preexisting ALT or AST or total bilirubin values above the upper limit of normal, the following threshold values should be used:
         i. For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).
         ii. For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal or ≥3 times the upper limit of normal (whichever is smaller).

D. Myelosuppression (Anemia, Neutropenia, Leukopenia) considered clinically significant by the investigator.
E. Hemorrhage considered clinically significant by the investigator
F. Infection
G. Skin disorders (Rash) considered clinically significant by the investigator
H. Clinically significant immunological events (Hypersensitivity)
I. Renal dysfunction (increased blood creatinine considered clinically significant by the investigator)
J. Pleural effusions
K. Clinically significant cardiac events (QT prolongation, atrial fibrillation, sinus bradycardia, tachycardia, supraventricular tachycardia, bradycardia, premature ventricular contractions, pericardial effusion, right bundle branch block, sinus tachycardia, or premature atrial contractions).

2) In relation to atezolizumab:
   A. Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see *EASL, 2019*)
   B. Suspected transmission of an infectious agent by the study treatment, as defined below

      Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

   C. Systemic lupus erythematosus
   D. Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, macrophage activating syndrome, hemophagocytic lymphohistiocytosis
   E. Nephritis
   F. Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
   G. Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
   H. Vasculitis
   I. Autoimmune hemolytic anemia
   J. Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

13.10 Information to Be Provided by the Investigator for a SAE or AESI

The following information about the patient and the event must be provided to the sponsor:

- Investigator identification,

- Patient identification (e.g., sex, age, date of birth, code),
- Information on study drug (e.g., start/stop date, dose and frequency of study drug administered),
- Description of event.

In addition to the above information, the sponsor will require the investigator's assessment of the following:

- Severity of the SAE or AESI,
- Relationship of the SAE or AESI to the study drug,
- Outcome of the SAE or AESI.

13.11 Follow-up Information on a SAE or AESI

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained by the investigator. For all SAEs or AESIs, the investigator must pursue and provide information to the sponsor. In addition, an investigator may be requested by the sponsor to obtain specific information in an expedited manner. This information may be more detailed than that captured on the AE form.

In general, this information will include a description of the AE, provided in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes, such as concomitant medication and illnesses, must also be provided.

13.12 Required Follow-up for SAEs or AESIs

Routine follow-up should be conducted through and including 28 days after the last administration of assigned study treatment in the trial or the investigator/patient decision to discontinue treatment, whichever occurs later, in all patients, in order to monitor the occurrence of SAEs or AESIs. After this time, ongoing AEs thought to be at least possibly study-drug related, as well as all ongoing SAEs, should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE, v5.0 grade ≤ 1), stabilize, or are considered to be chronic/irreversible. The medical monitor may specify a longer follow-up period if required to assure the safety of the patient.

13.13 Expedited Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

Study sponsor, Fundación Zero LMC, is responsible for reporting suspected, unexpected, serious adverse reactions involving the study drug to all regulatory authorities and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable.
The sponsor will notify investigators of all reportable SAEs. This notification will be in the form of an expedited safety report (ESR). Upon receiving such notices, the investigator must review and retain the notice with other study-related documentation.

Suspected serious adverse reactions and other significant safety issues reported from the investigational product development program will be reported by the sponsor or its designated representative—either as expedited safety reports and/or in aggregate reports—to the relevant, competent health authorities in all concerned countries.

13.14 Contraception and Pregnancy

Females of childbearing potential and fertile males will be informed of the potential risk of conception while participating in this study. Females of childbearing potential are required to use a highly effective form of contraception from recruitment through at least 4 months after the end of treatment (see inclusion criterion 7)

A pregnancy test will be performed on each premenopausal female of childbearing potential within 7 days prior to first dose of bosutinib, and again each month during the study, at the end-of-treatment visit and at the end-of-study visit. A negative pregnancy test must be documented prior to administration of study drug.

Females should be advised to take a pregnancy test if their period is late, and to inform their investigator of the result.

If a patient is confirmed pregnant during the trial, study drug administration must be discontinued immediately. The investigator must also immediately notify the sponsor medical monitor of this event and record the pregnancy on a pregnancy form. Initial information regarding a pregnancy must be immediately (in less than 24 hours) forwarded to FTH Pharmacovigilance and Risk Management or its designated representative.

The investigator must immediately report follow-up information to the sponsor regarding the course of the pregnancy, including perinatal and neonatal outcomes, regardless of whether the patient has discontinued participation in the study. If the pregnancy results in the birth of a child, additional follow-up information may be requested. If the pregnancy results in spontaneous abortion or stillbirth, that event should be reported as a SAE.

Pregnancy outcomes must also be collected for the female partners of any males who took study drug in this trial. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

13.15 Overdose, medication error, abuse, misuse

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of study treatment that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded and forwarded to FTH Pharmacovigilance and Risk Management or its designated representative within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded on the eCRF; dosing information is recorded on the form.

Other special situations such as medication error (including intercepted or potential medication error), abuse and misuse are not considered AEs. However, they should be also recorded and forwarded to FTH within 24 hours.

14 CO-TREATMENT AND TREATMENT SUPPLY

14.1 Prior and Concomitant Treatment

All concomitant medications administered from the time of informed consent signature until 28 days after end of treatment (either the last dose of study drug or the investigator/patient decision to discontinue, whichever occurs later), are to be recorded in the patient's eCRF.

14.2 Permitted Treatment

All routine and appropriate supportive care (including receipt of blood products and hematopoietic growth factors) will be allowed during this study, as clinically indicated, and in accordance with standard-of-care practices. Clinical judgment should be utilized in the treatment of any AE experienced by an individual patient.

Information on all concomitant medications, administered blood products, and interventions occurring during the study must be recorded on each patient's eCRF. Among other treatments for concurrent illnesses, the following therapies are allowed:

- Rhu-EPO and G-CSF are allowed in case of anemia (Hb<12 g/dl) and/or neutropenia (ANC < 1000/mm^3)
- Diuretics are allowed in case of fluid retention
- It may be necessary in some situations to administer corticosteroids, immunosuppressives, thyroid replacement hormone, anti-thyroid drug, insulin, antihistamine, anti-pyretic, epinephrine, bronchodilators, and oxygen in case of adverse events observed with atezolizumab.

14.3 Prohibited Treatments/Therapy

The following concurrent medications and treatments are prohibited:

- Other anticancer therapies
- Other investigational drugs or devices
- Medications that prolong the QT interval (see Appendix A)
- CYP3A inhibitors (including, but not limited to itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, telithromycin, nefazodone, mibefradil, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, boceprevir, telaprevir, grapefruit products including grapefruit juice) or moderate CYP3A inhibitors (including, but not limited to fluconazole, ciprofloxacin, erythromycin, diltiazem, verapamil, amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir, aprepitant, crizotinib, imatinib), and strong CYP3A inducers (including, but not limited to carbamazepine, phenytoin,

rifampicin, St. John's Wort), or moderate CYP3A inducers (including, but not limited to bosentan, efavirenz, etravirine, modafinil, nafcillin).

15 PLANNED STATISTICAL ANALYSIS

This is a phase Ib/II, single arm, open-label and dose-escalation study designed to determine the safety profile and the recommended phase III dose of bosutinib when administered in combination with atezolizumab in naïve patients with chronic myeloid leukemia in chronic phase.

15.1 Analysis Sets

15.1.1 Full Analysis Set

The full analysis set (FAS) comprises all patients who complete the first three phases of treatment (combination of bosutinib and atezolizumab) successfully.

15.1.2 Safety Set

The safety set (SS) includes all patients who received at least one dose of study medication. Reporting and analysis of safety information for these patients will be split into subsets by study phases.

15.1.3 Per-Protocol Set

The per-protocol set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol (CSP).

A compliance of 70% with bosutinib treatment will be necessary to be included in the PPS

Protocol deviations leading to exclusion from the PPS will be detailed in the Clinical Study Report.

15.2 Patient Demographics/other Baseline Characteristics

Demographic and other baseline data will be summarized descriptively for both the SS and the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be presented.

15.3 Primary Objective

The primary objective is to evaluate the safety profile of bosutinib 400 mg daily in combination with atezolizumab as first line treatments in participants with chronic myeloid leukemia.

15.3.1 *Analysis Set and Grouping for the Analyses*

The safety set population will be used for all safety analyses. Reporting of safety information for these patients will be split into subsets by first phase, second phase, third phase, and fourth phase.

15.3.2 *Adverse Events*

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs (TEAEs). However, all safety data (including those from the pre-treatment period) will be listed and those collected during the pre-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, causality relation to study treatment by the phases or subsets previously described.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and safety subset.

Specific safety event categories will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified safety event category, number and percentage of patients with at least one event part of the safety set will be reported. Also AESI will be summarized and analyzed.

15.3.3 *Laboratory Abnormalities*

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 the study's biostatistician and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned to all non-missing values not graded as 1 or higher. Grade 5 will not be used.

In some cases, (e.g., white blood cell differentials) the lower limits of normal ranges used in CTCAE definition have to be replaced by a clinically meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-safety subset summaries will be generated separately for hematology, and biochemistry tests:

- number and percentage of patients with clinically significant laboratory abnormalities, by parameter and worst post-baseline CTCAE grade. Each patient will be counted only for the worst grade observed post-baseline, regardless of the baseline status
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value

- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high
- classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

15.3.4 Other Safety Data

Other safety data collected (e.g., ECG, vital signs) will be listed and summarized using descriptive statistics as appropriate. Notable values will be flagged. Notable/Abnormal values for safety data will be further specified in the RAP.

15.3.5 Immunological Analysis

Treatment in vivo with TKI drugs may increase the cytotoxic response in CML patients, helping them to control the disease progression in the absence of treatment. The analysis of the progression of these patients will allow us to correlate the cytotoxic response developed by previous treatment with different TKIs with a CML relapse in order to describe new biomarkers that may predict a successful treatment interruption in these patients.

15.3.5.1 Immunological Assays:

1. Phenotypic Assays: 6 samples per patient

a. Cell characterization: NK cells (CD3- CD56+; CD16+ CD56+; TNFα; IFNα; Granzyme b NK-LGL cells (CD56+ CD57+), T-LGL cells (CD3+ CD57+), CD8 TCRα/β, NK markers (NKG2D, KIR2DL2/DL3/DS2, KIR2DL5B).

b. Differentiation and maturation (NKG2A/CD16) and proliferation (NK67) markers of NK cells.

c. CD4+ T cells activation markers: CD25 CD69 HLA-DR.

d. Predictive markers of CML relapse: T regs (CD4+ CD25int-hi CD127low), CD8+ T cells (PD-1/PD-L1) and plasmacytoid dendritic cells (CD86+).

15.4 Secondary objectives

15.4.1 Secondary efficacy variables:

- To evaluate the Major Molecular Response (MMR) and Molecular Response (MR) rates at 3, 6, 12 months and at the End of Treatment (EoT) visit. Based on:
  - MMR is defined as ≥ 3-log reduction in BCR-ABL transcripts or a ratio of <= 0.1% on the International Scale (IS)
  - Molecular Response (MR): As defined in section 4. Definition of Terms
- Percentage of Participants Alive at Month 6, 12 at the EoT visit.
- Number of confirmed MR4 and MR4.5. [at end of treatment]

- The rate of confirmed MR4 and MR4.5 at the end of treatment.
- Number of Complete Cytogenetic Responses (CCyR) [Time Frame: After one year from study entry]
- The rate of Complete Cytogenetic Response (CCyR) at 1 year.
- Number of days to response (CCyR, MMR, MR4, MR4.5). [Time Frame: at the EoT visit]
- The median time to response and the overall estimated probability of response (CCyR, MMR, MR4, MR4.5).
- Number of overall surviving patients [Time Frame: at the EoT visit]
- Number of progression-free survival patients. [Time Frame: at the EoT visit]
- Number of failure-free survival patients. [Time Frame at the EoT visit]
- Number of event-free survival patients.[Time Frame: at the EoT visit]
- Immunological Studies

15.4.2 Analyses Methods for Secondary Objectives

A descriptive analysis of the secondary objectives will be carried out. Qualitative variables will be summarized by counts and percentages. Quantitative variables will be summarized by means of mean, standard deviation, minimum, maximum and main quartiles. The 95% confidence intervals will also be calculated.

The hypothesis of normality will be tested by the Shapiro-Wilk test. A repeated measurement ANOVA or its equivalent non-parametric test will be used depending on the result of this test. The qualitative variables will be analyzed by means of the Fisher Chi-square test/exact test or Cochran's Q test, as appropriate.

Survival analysis will be performed using the Kaplan-Meier estimation method and the Log-rank test. A p-value of <0.05 will be considered statistically significant.

15.5 Sample Size Calculation

There will be no formal calculation of the sample size. The sample size is selected to allow sufficient data collection for the DLT and safety assessment. It is an exploratory study. The minimum number of patients for the DLT evaluation will be 10 if no DLT is observed. After MTD is calculated, 26 more patients will be recruited for the dose variation phase. 36 patients (both, a first group of 10 patients and a second of 26 patients) will receive bosutinib 400 mg/day in monotherapy during one cycle of treatment. According to previous experience (*Tim H Brümmendorf et al, 2015; Jorge E. Cortes el al, 2018*), we assume that, at most, 15% of the patients included will not enter the dose escalation phase after the first month of treatment with bosutinib, due to side effects. Consequently, a total of 30-31 patients will receive the combination of bosutinib plus atezolizumab.

16 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor/CRO has implemented and maintains a quality assurance system with written SOPs to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

The sponsor performs quality control and assurance checks on all clinical studies that it sponsored. Before enrolling any patients into this study, the sponsor or its designee, as well as the investigator, will review the protocol, the Clinical Investigator's Brochure; the eCRF model and the instructions for its completion; the procedure for obtaining informed consent; and the procedure for reporting AEs. A qualified representative of the sponsor will monitor the conduct of the study by both visiting the site and contacting it by telephone or email. During the visits, information recorded in the eCRFs will be verified against source documents. The sponsor's medical monitor will review the data for safety information. The sponsor's clinical research associates (CRAs) will review the data for legibility, completeness, and logical consistency. Additionally, the sponsor's CRAs and quality control staff will identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be added to the electronic database and reviewed by the investigational site for resolution. The sponsor may visit the investigational site and perform a quality check of the eCRFs against source documents.

16.1 Investigators and Study Administrative Structure

The investigator must provide the sponsor with the following documents before enrolling any patient:

- A clinical trial agreement
- Documentation of financial disclosure
- Principal investigator's *curriculum vitae*

If any investigator retires, relocates, or otherwise withdraws from conducting the study, the responsibility for maintaining records shall be transferred to another person (e.g., sponsor, IRB/IEC, or other investigators) who accepts the responsibility. The sponsor must be notified in writing and agree to the change in advance.

16.2 Study Monitoring

This study will be monitored by representatives of the sponsor. Site visits will be made before the study begins, at regular intervals during the study, and at the study closeout. Communication by telephone, mail, and e-mail may be used, as needed, to supplement site visits. The investigator and the rest of the investigational team will cooperate with the sponsor, provide all appropriate documentation, and be available to discuss the study. Adequate time and space for these visits should be stablished in agreement with the investigator. The purpose of the site visits is to verify:

- Adherence to the protocol (the investigator should document and explain any deviation from the approved protocol)
- The completeness and accuracy of the data registered in the eCRFs and the dispensing and inventory records of the study medication and other study supplies
- Compliance with regulations
- These verifications will require comparison of the source documents to the eCRFs
- The scope, frequency and relevant details regarding the study monitoring will be detailed in the monitoring plan

17 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with the ethical standards that have their origin in the Declaration of Helsinki and that are consistent with GCP guidelines and the applicable regulatory requirements.

17.1 Institutional Review Board or Ethics Committee Approval

The protocol and the ICF must have the approval of an IRB/IEC. The signed IRB/IEC approval letter must identify the documents approved (e.g., list the investigator's name, the protocol number and title, the date of the protocol and informed consent document, and the date of approval of the protocol and the informed consent document). Any advertisements used to recruit patients should also be reviewed by the IRB/IEC. The sponsor will not ship clinical supplies until a signed approval letter from the IRB/IEC has been received and a Clinical Trial Agreement has been signed by the sponsor and the clinical site.

17.2 Patient Information and Consent

Regulatory agencies have issued regulations to provide protection for human patients in clinical investigations and to describe the general requirements for informed consent.

A copy of the study ICF should be submitted to the sponsor for review and comment before its submission to the IRB/IEC. The study should not begin until the ICF has been reviewed and approved by the sponsor, and must not begin until the document has been approved by the IRB/IEC.

The ICF shall contain all the elements of the informed consent specified in the regulations. Some regulations may require the disclosure of additional information to the patient and/or inclusion of additional information in an informed consent document.

Nothing in this protocol or the regulations is intended to limit the authority of a physician to provide emergency medical care under applicable regulations. In addition, the investigator should be aware that some regulations require that he/she permits regulatory agencies to conduct inspections and review records pertaining to this clinical investigation.

17.3 Patient Confidentiality

The investigator must ensure anonymity of the patients; patients must not be identified by their names in any documents submitted to sponsor. Signed informed consent forms and identification patient enrollment log must be kept strictly confidential while allowing patient identification at the site.

17.4 Publication of the Study Protocol and Results

The sponsor ensures that the key design elements of this protocol will be posted in REec and any other publicly accessible database such as clinicaltrials.gov, if necessary in addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in REec and other public accessible database of clinical study results.
In addition, the sponsor may also publish the results in conferences and medical journals when deemed appropriate.

17.5 Study Documentation

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Fundación Zero LMC-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, inspections and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site, under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study, but it will not be source of any of the data collected. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data recorded in the eCRFs and all other required reports. Data recorded in the eCRF should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF

must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) must be retained for a period of not less than twenty-five (25) years from the completion of the Clinical Trial, or longer if required by applicable regulation or the sponsor requires their retention for an additional period of time.

17.6 Confidentiality of Study Documents

All unpublished information that the sponsor provides to the investigator, as well as all information generated in connection with the study, must be kept confidential and must not be disclosed to a third party without the prior written consent of the sponsor. In addition, this information must not be published prior to the sponsor's review, in accordance with the terms of the Clinical Trial Agreement.

17.7 Audits and Inspections

Source data/documents must be readily available and accessible, upon request, to the Sponsor, or its designee, or to the Health Authorities.

17.8 Financial Disclosures

Financial disclosures should be provided prior to the start of the study by study personnel who are directly involved in the treatment or evaluation of patients at the site.

17.9 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its agents, if any, monitoring the study to request approval of a protocol deviation, as no unauthorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by sponsor and approved by the IRB/IEC/REB it cannot be implemented except when necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial. All significant protocol deviations will be recorded and reported in the CSR.

17.10 Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by sponsor and investigators. Protocol modifications that are considered

substantial, must be approved by sponsor, investigators, Health Authorities, and the IRB/IEC/REB when required.

Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the IRB/IEC and authorities at the study site should be informed according to local regulations.

18 DATA HANDLING AND RECORD KEEPING

18.1 Case Report Forms and Study Records

Study-specific eCRF will be made available to the investigative sites. Study data, contained in source documentation, will be recorded into the eCRFs, that will not be source of any data, for all patients screened for the study. All pertinent data records will be submitted to the sponsor during and/or at completion or termination of the study.

18.2 Access to Source Documentation: Data Confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require that all subjects recruited sign an authorization (ICF) that informs them about the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their protected health information (PHI).

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, will retain the ability to use all information collected prior to the revocation of the authorization. For subjects that have revoked authorization to collect or use PHI, reasonable attempts should be made to obtain permission to collect follow-up safety information (e.g., has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study (eCRD) uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

18.3 Site Monitoring

Before study initiation, the clinical monitor will review the protocol and eCRF model with the investigators and their staff, if apply. During the study, the clinical monitor will visit the site regularly to verify the source documents data entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to verify that study treatments are being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the clinical monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. The clinical monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

18.4 Data Collection

The designated investigator staff will enter the data required by the protocol into an electronic case report form (eCRF). Investigator site staff will not be given access to the eCRF system until they have been trained in its use. Automatic validation checks for data discrepancies in the eCRFs will be implemented and, it will allow modification or verification of the entered data by the investigator staff while maintaining data traceability.

The principal investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

18.5 Database Management and Quality Control

The Sponsor or person to whom this function is delegated will review the data entered by investigational staff for completeness and quality. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the EDC system. Designated investigator site staffs are required to respond promptly to queries and to make any necessary changes to the data.

Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for Regulatory Activities (MedDRA) terminology.

After database lock, the investigator will receive copies of the patient data, either in paper or in electronic format, for archiving at the investigational site.

18.6 Retention of Data

Trial documents (including relevant correspondence related to this clinical study, patient records, source documents, eCRFs, study drug inventory records; IRB/IEC and sponsor correspondence pertaining to the study; and original patient, laboratory, and study drug inventory records relating to the study) should be retained for at least 25 years after the end of the study, or a longer period if required by applicable regulatory requirements, ICH or by agreement with the sponsor. Thereafter, records will not be destroyed without giving the sponsor prior written notice and the opportunity to further store such records, at the sponsor's cost and expense.

18.7 Termination of Study

The sponsor may terminate the study or a study site at any time for any of the following reasons:

- Failure to enroll patients
- Protocol violations
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Questionable safety of the study drug
- Suspected lack of efficacy of the study drug
- Administrative decision

In the event of the termination of the study, by either the sponsor or an investigator:

- The investigator will return all study drugs, eCRFs, and related study materials to the sponsor.
- A written statement describing why the study was terminated prematurely will be provided by either the sponsor or the investigator.

19 REFERENCES

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APPENDIX A: Drug-induced QT prolongation and Torsades de Pointes

Four categories of QT-prolonging drugs that may be used as a guide for this protocol can be accessed at http://www.crediblemeds.org/everyone/composite-list-all-qtdrugs. Categories include "Drugs with Known TdP Risk," "Drugs with Possible TdP Risk," "Drugs with Conditional TdP Risk," and "Drugs to be Avoided by Congenital Long QT Patients." The investigator site should register (under the "For Healthcare Providers" tab) to access these categories. If the investigator site does not wish to register, a composite list, including all categories, is available.

Drugs with a known risk of *torsades de pointes* are listed in the table below, and are the only category of QT-prolonging drugs that are prohibited in this study.

Note: The website and table are only to be used as a guideline and are not comprehensive. It is the investigator's responsibility to ensure that any drugs under consideration have not been newly identified as causing *torsades de pointes*.

Table A-1: Drugs generally accepted by the QTDrugs.org Advisory Board of the Arizona CERT to have a known risk of causing *torsades de pointes*; prohibited in this study

Generic name	Brand names	Class / Clinical use
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic/abnormal heart rhythm
Arsenic trioxide	Trisenox®	Anticancer/Leukemia
Astemizole	Hismanal®	Antihistamine/Allergic rhinitis
Azithromycin	Zithromax®, Zmax®	Antibiotic/bacterial infection
Bepridil	Vascor®	Antianginal/heart pain
Chloroquine	Aralen®	Antimalarial/malaria infection
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic/Antiemetic/schizophrenia, nausea
Cisapride	Propulsid®	GI stimulant/heartburn
Citalopram	Celexa®	Antidepressant/depression
Clarithromycin	Biaxin®, Prevpac®	Antibiotic/bacterial infection
Cocaine	Cocaine	Local anesthetic/topical anesthetic
Disopyramide	Norpace®	Antiarrhythmic/abnormal heart rhythm
Dofetilide	Tikosyn®	Antiarrhythmic/abnormal heart rhythm
Domperidone	Motilium®, Motillium®, Motinorm®, Costi®, Nomit®	Antinausea/nausea
Dronedarone	Multaq®	Antiarrhythmic/atrial fibrillation
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Sedative; antinausea/anesthesia adjunct, nausea
Erythromycin	Erythrocin®, E.E.S. ®, Robimycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Tiloryth®	Antibiotic; GI stimulant/bacterial infection; increase GI motility

Generic name	Brand names	Class / Clinical use
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E®, Exodus®, Esto®, Seroplex®, Elicea®, Lexamil®, Lexam®, Entact®, Losita®, Reposil®, Animaxen®, Esitalo®, Lexamil®	Antidepressant/major depression, anxiety disorders
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic/abnormal heart rhythm
Halofantrine	Halfan®	Antimalarial/malaria infection
Haloperidol	Haldol®, Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol®, Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Antipsychotic/schizophrenia, agitation
Ibutilide	Corvert®	Antiarrhythmic/abnormal heart rhythm
Levomethadyl	Orlaam®	Opiate agonist/pain control, narcotic dependence
Mesoridazine	Serentil®	Antipsychotic/schizophrenia
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadone®	Opiate agonist/pain control, narcotic dependence
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic/bacterial infection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Somatostatin analog/nausea and vomiting
Pentamidine	Pentam®, NebuPent®	Antiinfective/pneumocystis pneumonia
Pimozide	Orap®	Antipsychotic/Tourette's tics
Probucol	Lorelco®	Antilipemic/Hypercholesterolemia
Procainamide	Pronestyl®, Procan®	Antiarrhythmic/abnormal heart rhythm
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Antiarrhythmic/abnormal heart rhythm
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general/anesthesia
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic/abnormal heart rhythm
Sparfloxacin	Zagam®	Antibiotic/bacterial infection
Terfenadine	Seldane®	Antihistamine/Allergic rhinitis
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Antipsychotic/schizophrenia
Vandetanib	Caprelsa®	Anticancer/thyroid cancer

APPENDIX B: National Cancer Institute Common Terminology Criteria for Adverse Events

The United States of America (USA) National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE, v5.0) can be found on the following website: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

This version of CTCAE is compatible at the AE term level where each CTCAE term is a Medical Dictionary for Regulatory Activities Terminology Lowest Level Term (MedDRA LLT). CTCAE version 5.0 includes 837 AE terms. Each AE term is associated with a 5-point severity scale.