CLINICAL STUDY PROTOCOL

Protocol Title: ASCiminib, with or without Dasatinib combination, as a 2nd-Line therapy to ADVANCE the Treatment for Chronic Myelogenous Leukemia in chronic phase (**ASC2ADVANCE**)

Clinical Trial Protocol No:	Ozmosis Study No. OZUHN-044 Novartis Study Code: CABL001ACA03T
Protocol Version #:	1.0
Protocol Date:	10-Feb-2026
Phase of Study:	II
Sponsor/Principal Investigator:	Dr. Dennis Kim, UHN
Investigational Agent:	Asciminib

Protocol History	
Original:	Version 1.0; dated 10-Feb-2026

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Sponsor's Agreement to Protocol Version 1.0, [10-Feb-2026]

Name of Authorized Personnel

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Title of Authorized Personnel

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Signature of Authorized Personnel: _____

Date of Approval: _____

DD-MMM-YYYY

STUDY SYNOPSIS

Study Title:	ASCiminib, with or without Dasatinib combination, as a 2nd-Line therapy to ADVANCE the Treatment for Chronic Myelogenous Leukemia in Chronic Phase
Short Title:	ASC2ADVANCE
Brief Summary:	This study aims to evaluate Asciminib (ASC) +/- Dasatinib (DAS) therapy as a second-line treatment option for chronic phase chronic myeloid leukemia (CML) patients who have failed or met warning criteria after front line TKI therapy for resistance (based on the ELN 2020 failure/warning criteria).
Study Design:	A phase II, open-label, multi-site trial
Primary Objective:	To evaluate the effectiveness of ASC as a second-line therapy in chronic phase CML patients after 24 weeks of treatment.
Secondary Objectives:	1. To evaluate the effectiveness of ASC as a second-line therapy in chronic phase CML patients after 12 and 48 weeks of treatment. 2. To evaluate the effectiveness of ASC + DAS as a second-line therapy in chronic phase CML patients with high-risk mutations after 12, 24 and 48 weeks of treatment. 3. To evaluate the safety of ASC +/- DAS when used as a second-line therapy
Study Duration:	Approximately 2.5 years, including 18 months of recruitment, and approximately 12 months of treatment (12 cycles of 4 weeks each cycle)
Patient Duration:	Approximately 13 months including up to 48 weeks of treatment, followed by a safety follow up visit one month after the last dose.
Study Sites:	Approximately 4 sites within Ontario
Planned Total Sample Size:	Approximately 45 patients will be enrolled
Investigational Product Administration:	Asciminib (ASC) will be administered PO either as monotherapy in patients with a standard mutation profile, or in combination with Dasatinib (DAS) (as per standard of care (SOC)) for patients with a high-risk somatic mutation profile. *Patients will be given 80 mg ASC PO daily for 28 days every 4 weeks (continuously) for a period up to 48 weeks.*

	Patients with a high risk mutation profile will receive 100 mg DAS PO daily in addition to ASC, starting at C2D1.
Patient Population:	Adult patients diagnosed with CML, who have experienced treatment failure (i.e. resistance or suboptimal response) to first-line TKI therapy.
Inclusion/Exclusion Criteria:	**Inclusion Criteria** 1. Patients ≥18 years of age 2. Diagnosis of CML in chronic phase as per WHO criteria based on the presence of *BCR::ABL1* fusion gene by PCR at original diagnosis. Confirmation is recommended, if possible, by demonstrating the Philadelphia chromosome or variants by cytogenetics or FISH (Fluorescence In Situ Hybridization) in addition to bone marrow morphology confirming CML-CP. Patients with additional chromosomal abnormalities in addition to the Philadelphia chromosome are eligible. NGS testing at initial diagnosis is not required. 3. Warning or failure to first line of TKI therapy at the time of screening due to resistance or suboptimal response (based on the ELN 2020 failure criteria) 4. *BCR::ABL1* transcript type is trackable with institutional RQ-PCR (Real-time Quantitative Polymerase Chain Reaction) testing for response assessment 5. No prior or concurrent malignancies, except for adequately treated non-melanoma skin cancer, cervical carcinoma-in-situ, adequately treated Stage I or II cancer from which patient is in complete remission, or any other cancer from which patient has been disease free for a minimum of five years 6. Patients must be ASC naïve 7. Agree to conduct somatic mutation profile testing at enrollment 8. Adequate organ function defined by:

	- Creatinine clearance level ≥ 30 mL/min as calculated using the Cockcroft-Gault formula - Total bilirubin (TBL) ≤ 3.0 ULN without AST/ALT increase; participants with Gilbert's syndrome may only be included if TBL ≤ 3.0 x ULN or direct bilirubin ≤1.5 x ULN - Aspartate transaminase (AST) ≤ 5.0 x ULN - Alanine transaminase (ALT) ≤ 5.0 x ULN - Alkaline phosphatase (ALP) ≤ 2.5 x ULN - Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN and ≤ 1.5 x ULN, value should be considered not clinically significant and not associated with risk factors for acute pancreatitis 9. Women of childbearing potential (defined as all women physiologically capable of becoming pregnant) and fertile men must agree to use adequate contraception from the time of signing the informed consent form and for at least 7 days following the last dose of study treatment. Women are considered post-menopausal and *not* of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age, history of vasomotor symptoms). Acceptable methods of contraception include the following (applicable to the patient and/or patient's partner(s)): a. Total abstinence b. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In the case of oral contraception use, women should have been stable on the same pill for a minimum of 3 months before taking study drug.

	c. Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy or bilateral 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 by follow up hormone level assessment. d. Male sterilization (at least 6 months prior to screening). A vasectomized male partner should be the sole partner for that patient. Note that a negative pregnancy test is required for all women of childbearing potential at the time of study entry. **Exclusion Criteria** 1. Failure to provide informed consent 2. Prior stem cell or bone marrow transplant 3. Previous diagnosis of CML in accelerated phase (AP) or blast crisis (BC) 4. Known second chronic phase of CML after previous progression to AP/BC 5. ECOG performance status ≥3. 6. Any **one** of the following cardiac symptoms: a. History of myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, or coronary stent placement within the past six months b. Uncontrolled angina or uncontrolled congestive heart failure (NYHA class III or IV) within the past six months. c. Diagnosed congenital long QT syndrome d. Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes)

	e. Clinically significant, uncontrolled atrial fibrillation or other clinically relevant arrhythmias requiring ongoing intervention. f. Prolonged QTc interval on pre-entry electrocardiogram. Specifically, QTcF and QTc ≥ 450ms for male patients or ≥ 460ms for female patients. To be reported as the average of three serial baseline ECGs (using the QTcF formula) as determined by central reading. If QTcF ≥ 450 ms and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-screened for QTc. g. Subjects with hypokalemia or hypomagnesemia if it cannot be corrected prior to DAS administration. 7. Concurrent medical condition, which may increase the risk of toxicity including but not limited to: Pleural or pericardial effusion of any grade and pulmonary arterial hypertension. 8. History of significant bleeding disorder unrelated to cancer, including any of the following: a. Diagnosed congenital bleeding disorder (e.g., von Willebrand's disease) b. Diagnosed acquired bleeding disorder within one year (e.g., acquired antifactor VIII antibodies). c. Ongoing or recent (≤ 3 months) significant gastrointestinal bleeding 9. Presence of ASC resistant ABL1 KDM (Myristolyate site mutation, T315I, M244V, V299L, F359) using institutional Sanger sequencing test in each center as a SOC (if the ABL1 KDM result is available). 10. History of first line TKI discontinuation (with optimal response) due to adverse events

	including hematologic or non-hematologic toxicities 11. History of recurrent or chronic pancreatitis 12. Treatment with strong inducers of CYP3A is not allowed and should be switched to an alternative at least one week prior to the start of study treatment 13. Pregnant or nursing (lactating) women 14. Participation in a prior investigational study within 30 days prior to enrolment, or within 5 half-lives of the investigational product, whichever is longer. 15. Known central nervous system infiltration (in absence of suspicion of CNS involvement, lumbar puncture not required). 16. Known history of chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBc Ab/anti HBc) will be performed at screening. If anti-HBc is positive, HBV-DNA evaluation must be carried out at screening. Patients having positive HBV-DNA or positive HBsAg must not be enrolled in the study. 17. Patients with a known hypersensitivity to ASC or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. 18. Patients with a known hypersensitivity to DAS or to any component of APO-DASATINIB.
Study Assessments	Study assessments are depicted in the Study Schedule (Appendix I).
Response Assessment:	Major Molecular Response (MMR), defined as a 3-log reduction or deeper (0.1% International Scale) after 3, 6 and 12 cycles.
Statistical Analysis:	Refer to Section 11

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ABL1	Abelson murine leukemia viral oncogene homolog 1
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
AP	Accelerated Phase
AS/MTFs	Activated Signaling and Myeloid Transcription Factors
ASC	Asciminib
AST	Aspartate transaminase
BCR	Breakpoint Cluster Region
BC	Blast Crisis
CBC	Complete Blood Count
CCyR	Complete Cytogenetic Response
CML	Chronic Myeloid Leukemia
CP	Chronic Phase
CRF	Case Report Form
CT	Clinical Trial
DAS	Dasatinib
DILI	Drug-Induced Liver Injury
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELTS	EUTOS Long-Term Survival
EORTC	European Organization for Research and Treatment of Cancer
EUTOS	European Treatment and Outcome Study
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
HF	Heart Failure
ICF	Informed Consent Form
KD	Kinase Domain
LFTs	Liver Function Tests
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MMR	Major Molecular Response

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next-Generation Sequencing
Ph	Philadelphia Chromosome
PLT	Platelets
PMDA	Pharmaceuticals and Medical Devices Agency
PO	By Mouth
QI	Qualified Investigator
QoL	Quality of Life
RCT	Randomized Clinical Trial
REB	Research Ethics Board
RQ-PCR	Real-time Quantitative Polymerase Chain Reaction
SAE	Serious Adverse Event
STAMP	Specifically Targets the ABL Myristoyl Pocket.
SOC	Standard of Care
TKI	Tyrosine Kinase Inhibitor
TSH	Thyroid Stimulating Hormone
UHN	University Health Network
ULN	Upper Limit of Normal

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1. BACKGROUND and RATIONALE

1.1. Pathogenesis of chronic myeloid leukemia

Chronic Myelogenous Leukemia (CML) is a clonal myeloproliferative disorder characterized by the overproduction of leukemic myeloid cells with a consequence of *BCR::ABL1* gene rearrangement. The hallmark of CML is the Philadelphia (Ph) chromosome, found in up to 95% of patients[1]. The Ph chromosome results from a reciprocal translocation of chromosomes 9 and 22, i.e. t(9;22)(q34;q11), which fuses a portion of the Abelson (ABL1) gene on chromosome 9, with a portion of the breakpoint cluster region (BCR) gene on chromosome 22. This translocation creates the *BCR-ABL* fusion protein, a constitutively active cytoplasmic tyrosine kinase that increases signaling activity and affects the growth and differentiation of hematopoietic cells, allowing them to escape constraints on normal growth and become leukemic [2].

Most patients are diagnosed in the chronic phase (CP), characterized by anemia, splenomegaly, and leukocytosis, generally, with few constitutional symptoms such as fatigue, weight loss, malaise, easy satiety, and left upper quadrant fullness or pain. CML can progress to the accelerated phase (AP) or blast crisis (BC), often following worsening anemia, splenomegaly, and organ infiltration. Without treatment, around 25% of patients may transition into BC without a preceding AP [3,4].

1.2. Tyrosine kinase inhibitor therapy in the treatment of CML

The introduction of the Tyrosine Kinase Inhibitor (TKI), imatinib (Glivec®), in 2001 revolutionized the treatment of CML. Subsequently, several second-generation (2G) TKI agents, including dasatinib (DAS), nilotinib, and bosutinib, have been approved for first-line treatment of CML. TKI treatment has significantly improved survival rates for CML patients, with optimal responders achieving near-normal life expectancy [5].

Treatment guidelines recommend selecting the TKI based on individual patient and disease characteristics, including risk scores (Sokal, Hasford (Euro), EUTOS, or ELTS), preexisting comorbidities, and concomitant medications [6-8].

Despite advancements in TKI therapy, many patients with CML fail to respond adequately to their first-line TKI treatment, either due to resistance or intolerance. There remains an unmet need in identifying the optimal strategy for selecting second- or later-line TKI therapy. Identifying patients at higher risk of failing second-line treatment, and exploring whether this risk can be reduced through combination therapies or dose intensification is critical for improving patient outcomes. Current practice suggests that approximately half of the patients with CML will have received a second-generation TKI as first-line therapy. Moreover, somatic mutations develop in approximately 40% of these patients, highlighting the need for more effective and alternative therapeutic agents [9].

Selecting the appropriate treatment is critical to achieving early optimal responses, reducing the risk of disease progression, maintaining quality of life, and minimizing serious side effects.

1.3. Asciminib as a novel agent for the treatment of CML

ASC is a novel, oral, potent inhibitor of *BCR::ABL1* with a distinct mechanism of action that differentiates it from traditional TKIs. Unlike other *BCR-ABL* targeting TKIs that interact with the ATP-site on the SH1 domain in *ABL1* protein, ASC specifically targets the ABL myristoyl pocket (STAMP) in the *ABL1* protein. By occupying this binding site, ASC restores the negative regulation of kinase activity on the *ABL1* protein. ASC has also shown high selectivity against *BCR-ABL*-positive cell lines compared to other TKIs [10,11]. Most adverse effects associated with TKIs are due to off-target activity beyond *BCR-ABL* inhibition, which the specificity of ASC has been shown to minimize [12,13]. ASC was granted accelerated approval by the US FDA in October 2021 for adult patients with Ph+ CML-CP previously treated with two or more TKIs, and for those with the T315I mutation. It was also approved by the Japan Pharmaceuticals and Medical Devices Agency (PMDA) in March 2022 for CML treatment resistant or intolerant to previous therapy.

Overall, ASC has shown a favorable benefit-risk profile. Results from phase I (CABL001X2101) and ASCEMBL (CABL001A2301) studies demonstrated its superior efficacy in the heavily pretreated patients when compared to bosutinib [6,14]. Additionally, ASC demonstrated a superior efficacy and a favorable safety profile in newly diagnosed chronic-phase CML patients in the ASC4FIRST trial [15]. However, ASC has only recently been approved for use as a first and second line treatment in Canada. Refer to the ASC product monograph for a list of updated risks.

Specifically, ASC has shown notable advantages when compared to bosutinib, including higher rates of major molecular response (MMR; 25.5% vs. 13.2%) and complete cytogenetic response (CCyR; 44.4% vs. 20.8%). ASC also has a lower probability of discontinuation due to lack of efficacy (24.2% vs. 35.5% at week 96) or adverse events (7.0% vs. 25.0%), as well as a higher rate of event-free survival (57.4% vs. 25.2% at week 96). However, 24.2% of patients on ASC monotherapy still experience lack of efficacy. Importantly, 56% of the 39 patients who discontinued ASC due to lack of efficacy had new or persistent ABL1 kinase domain mutations, including those at ATP-binding or myristoyl pocket site mutations. This indicates that ASC alone may not be sufficient to completely overcome TKI resistance, particularly in patients with extensive prior TKI exposure [15].

1.4. Adverse impact of somatic mutation profiles on treatment outcomes in CML patients

Our research along with that of others [16,17], has highlighted that somatic mutations – particularly in activated signaling and myeloid transcription factors (AS/MTFs) – are associated with poorer outcomes following TKI therapy. Based on genetic analyses from the ASCEMBL study, the adverse impact of somatic mutations does not appear to be mitigated by ASC alone when compared to bosutinib [18].

1.5. Promises of combination treatment of Asciminib with other ATP biding pocket inhibitors

In vitro studies show that different BaF3 cell lines with ABL1 mutations have varying sensitivity to ASC [19]. Combining ASC with ATP binding pocket inhibitors, such as ponatinib or DAS, showed synergistically enhanced cytotoxicity compared to the inhibitors alone [19].This suggests a potential for synergistic effects when combining ASC with other TKIs, particularly with DAS or ponatinib.

1.6. Rationale of the present study design

Despite its promise, several knowledge gaps remain. Specifically, the effectiveness of ASC as a second-line therapy and the potential for combination therapy with DAS to overcome the adverse impact of somatic mutations are to be further investigated.

The ASC dose of 80 mg QD for patients with newly diagnosed CML-CP is based on the clinical experience in patients with CML-CP in studies CABL001X2101 and CABL001A2301 and the PK/Pharmacodynamic (PD) modelling based exposure-response and exposure-safety analyses. Importantly, ASC 80 mg QD is the dose currently approved for patients with CML-CP, making it the most clinically relevant and regulatory-supported dose for this trial.

The treatment period is designed to allow for adequate assessment of both molecular and hematologic responses, which may require prolonged therapy given the chronic nature of CML and the time-dependent depth of molecular responses observed with TKIs. A minimum treatment duration of 12-36 weeks has therefore been chosen to enable a robust evaluation of early molecular milestones (e.g., BCR::ABL1 ≤10% at 3 months) and sustained responses, while also ensuring sufficient safety data are captured.

This design will provide critical evidence regarding the potential of ASC in combination with DAS to overcome resistance mechanisms, achieve faster and deeper molecular responses, and ultimately improve long-term outcomes for patients with CML-CP.

2. STUDY DESIGN

This study is designed as a prospective study, focusing on a cohort of patients diagnosed with CML, who have experienced treatment failure (i.e. resistance or suboptimal response) to first-line TKI therapy. Eligible patients who provide consent will initiate treatment with ASC at 80 mg daily as a second-line therapy. Upon enrollment, somatic mutation profiling will be performed through the central lab for next-generation sequencing (NGS) test. Patients with a high-risk mutation profile who tolerate ASC for 4 weeks, will receive, in addition to ASC, DAS 100 mg daily, administered as per standard of care (SOC). Patients will continue on ASC 80 mg daily (with or without DAS), with potential dose adjustments based on adverse events.

1) Patients *without* a high-risk mutation profile will receive ASC monotherapy at a dose of 80 mg daily, in 28-day cycles, administered every 4 weeks.
2) Patients *with* a high-risk mutation profile will receive ASC 80 mg daily for the first 4 weeks (Cycle 1), followed by a combination of ASC 80 mg + DAS 100 mg daily starting from Cycle 2 onward.

To assess response, a minimum of 3 and a maximum of 12 cycles (up to 48 weeks) will be given for both groups.

2.1. Study Schema

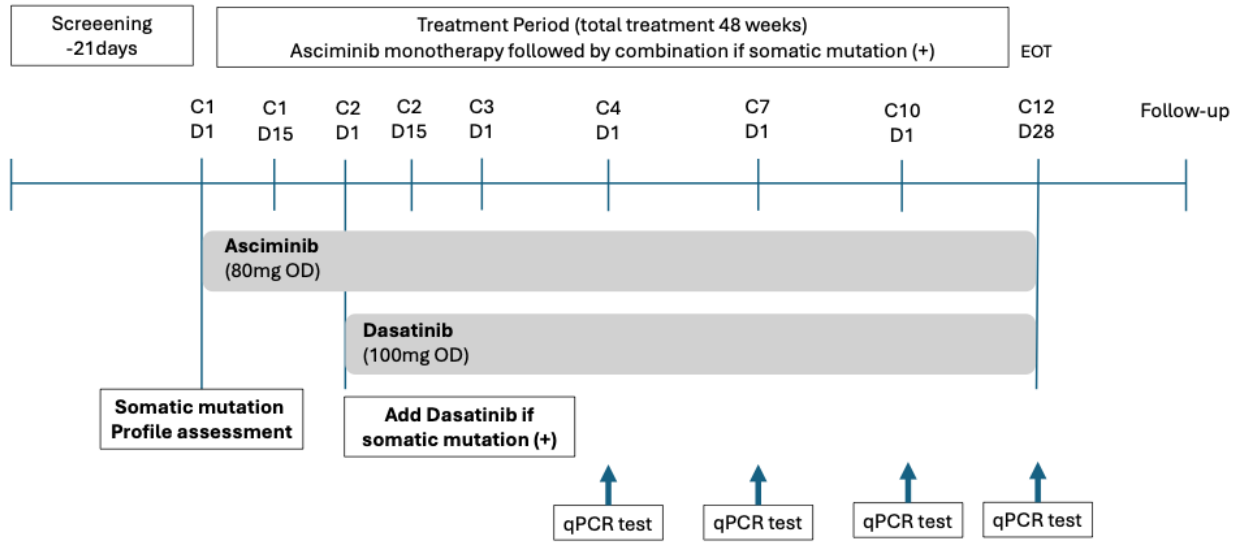

Figure 1. Summary of study concept for high-risk mutation profile-based stratification of treatment arms into ASC 80 mg daily monotherapy vs combination of ASC 80 mg daily with DAS 100 mg daily. Each cycle is 28 days in length, administered every 4 weeks, for a maximum total duration of 48 weeks.

2.2. Sample Size

Approximately 45 adult patients will be enrolled in this study.

2.3. Study Objectives

Table 1: Study objectives and endpoints

Primary Objective	Primary Endpoint
To evaluate the effectiveness of ASC as a second-line therapy in chronic phase CML patients after 24 weeks of treatment.	The proportion of patients achieving Major Molecular Response (MMR), defined as a 3-log reduction or deeper (0.1% International Scale), after 24 weeks (**6** cycles) of treatment with ASC as a second-line therapy.
Secondary Objectives	**Secondary Endpoints**
To evaluate the effectiveness of ASC as a second-line therapy in chronic phase CML patients after 12 and 48 weeks of treatment.	The proportion of patients achieving MMR, defined as a 3-log reduction or deeper (0.1% International Scale), after 12 and 48 weeks (**3** and **12** cycles) of treatment with ASC as a second-line therapy.
To evaluate the effectiveness of ASC + DAS as a second-line therapy in chronic phase CML patients with high-risk mutations after 12, 24 and 48 weeks of treatment.	The proportion of patients achieving MMR with ASC + DAS, defined as a 3-log reduction or deeper (0.1% International Scale), after 12, 24 and 48 weeks (**3**, **6** and **12** cycles) of treatment
To evaluate the safety of ASC +/- DAS when used as a second-line therapy	1. Rate of discontinuation of treatment due to adverse events 2. Rate of patients requiring dose adjustments due to adverse events 3. Rate of grade 3 or 4 AEs in all patients 4. Type, frequency and severity of all adverse events

3. PATIENT SELECTION

3.1. Eligibility

This trial will be conducted in compliance with the protocol, GCP and applicable regulations. Eligibility status must be confirmed by a Qualified Investigator (QI) or designate prior to enrollment. It is important that no exception is to be made to the eligibility criteria. Questions related to eligibility requirements must be discussed with Ozmosis and/or QI prior to enrollment.

3.1.1. Inclusion Criteria

For inclusion in this study, patients must fulfill all the following criteria:

1. Patients ≥18 years of age
2. Diagnosis of CML in chronic phase as per WHO criteria based on the presence of *BCR::ABL1* fusion gene by PCR at original diagnosis. Confirmation is recommended, if possible, by demonstrating the Philadelphia chromosome or variants by cytogenetics or FISH (Fluorescence In Situ Hybridization) in addition to bone marrow morphology confirming CML-CP. Patients with additional chromosomal abnormalities in addition to the Philadelphia chromosome are eligible. NGS testing at initial diagnosis is not required.
3. Warning or failure to first line of TKI therapy at the time of screening due to resistance or suboptimal response (based on the ELN 2020 failure criteria)
4. *BCR::ABL1* transcript type is trackable with institutional RQ-PCR (Real-time Quantitative Polymerase Chain Reaction) testing for response assessment
5. No prior or concurrent malignancies, except for adequately treated non-melanoma skin cancer, cervical carcinoma-in-situ, adequately treated Stage I or II cancer from which patient is in complete remission, or any other cancer from which patient has been disease free for a minimum of five years
6. Patients must be ASC naïve
7. Agree to conduct somatic mutation profile testing at enrollment
8. Adequate organ function defined by:

- Creatinine clearance level ≥ 30 mL/min as calculated using the Cockcroft-Gault formula
- Total bilirubin (TBL) ≤ 3.0 ULN without AST/ALT increase; participants with Gilbert's syndrome may only be included if TBL ≤ 3.0 x ULN or direct bilirubin ≤1.5 x ULN
- Aspartate transaminase (AST) ≤ 5.0 x ULN
- Alanine transaminase (ALT) ≤ 5.0 x ULN
- Alkaline phosphatase (ALP) ≤ 2.5 x ULN
- Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN and ≤ 1.5 x ULN, value should be considered not clinically significant and not associated with risk factors for acute pancreatitis

9. Women of childbearing potential (defined as all women physiologically capable of becoming pregnant) and fertile men must agree to use adequate contraception from the time of signing the informed consent form and for at least 7 days following the last dose of study treatment. Women are considered post-menopausal and *not* of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age, history of vasomotor

symptoms). Acceptable methods of contraception include the following (applicable to the patient and/or patient's partner(s)):

a. Total abstinence
b. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In the case of oral contraception use, women should have been stable on the same pill for a minimum of 3 months before taking study drug.
c. Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy or bilateral 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 by follow up hormone level assessment.
d. Male sterilization (at least 6 months prior to screening). A vasectomized male partner should be the sole partner for that patient.

Note that a negative pregnancy test is required for all women of childbearing potential at the time of study entry.

3.1.2. Exclusion Criteria

1. Failure to provide informed consent
2. Prior stem cell or bone marrow transplant
3. Previous diagnosis of CML in accelerated phase (AP) or blast crisis (BC)
4. Known second chronic phase of CML after previous progression to AP/BC
5. ECOG performance status ≥3.
6. Any **one** of the following cardiac symptoms:
   a. History of myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, or coronary stent placement within the past six months
   b. Uncontrolled angina or uncontrolled congestive heart failure (NYHA class III or IV) within the past six months.
   c. Diagnosed congenital long QT syndrome
   d. Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes)
   e. Clinically significant, uncontrolled atrial fibrillation or other clinically relevant arrhythmias requiring ongoing intervention.
   f. Prolonged QTc interval on pre-entry electrocardiogram. Specifically, QTcF and QTc ≥ 450ms for male patients or ≥ 460ms for female patients. To be reported as the average of three serial baseline ECGs (using the QTcF

formula) as determined by central reading. If QTcF ≥ 450 ms and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-screened for QTc.

g. Subjects with hypokalemia or hypomagnesemia if it cannot be corrected prior to DAS administration.

7. Concurrent medical condition, which may increase the risk of toxicity including but not limited to: Pleural or pericardial effusion of any grade and pulmonary arterial hypertension.
8. History of significant bleeding disorder unrelated to cancer, including any of the following:
    a. Diagnosed congenital bleeding disorder (e.g., von Willebrand's disease)
    b. Diagnosed acquired bleeding disorder within one year (e.g., acquired antifactor VIII antibodies).
    c. Ongoing or recent (≤ 3 months) significant gastrointestinal bleeding
9. Presence of ASC resistant ABL1 KDM (Myristolyate site mutation, T315I, M244V, V299L, F359) using institutional Sanger sequencing test in each center as a SOC (if the ABL1 KDM result is available).
10. History of first line TKI discontinuation (with optimal response) due to adverse events including hematologic or non-hematologic toxicities
11. History of recurrent or chronic pancreatitis
12. Treatment with strong inducers of CYP3A is not allowed and should be switched to an alternative at least one week prior to the start of study treatment
13. Pregnant or nursing (lactating) women
14. Participation in a prior investigational study within 30 days prior to enrolment, or within 5 half-lives of the investigational product, whichever is longer.
15. Known central nervous system infiltration (in absence of suspicion of CNS involvement, lumbar puncture not required).
16. Known history of chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBc Ab/anti HBc) will be performed at screening. If anti-HBc is positive, HBV-DNA evaluation must be carried out at screening. Patients having positive HBV-DNA or positive HBsAg must not be enrolled in the study.
17. Patients with a known hypersensitivity to ASC or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container.
18. Patients with a known hypersensitivity to DAS or to any component of APO-DASATINIB.

4. PATIENT SCREENING AND ENROLLMENT

Prior to screening patients, each site must have submitted all necessary regulatory documentation to Ozmosis and the site must have been activated by Ozmosis. Access to the electronic case report forms (eCRFs) will only be granted once this has been received.

All patients will be screened and confirmed to be eligible by a site QI, and consenting will occur according to the site's ethics board approved process, prior to the patient's enrollment into this study.

No patient can receive protocol treatment until eligibility has been confirmed and the Patient Enrollment Form has been submitted to Ozmosis. The Patient Enrollment Form must be completed, and signed by a QI prior to enrollment. There are 2 sections to the Patient Enrollment Form:

- SCREENING (top section): This section is completed by the site and should be e-mailed to ozmclinical@ozmosisresearch.ca or faxed to 416-634-8333 at the time of screening.

- ENROLLMENT (bottom section): This section is completed by the site at the time of enrollment. The site will submit the signed and completed Patient Enrollment Form to Ozmosis by e-mailing to ozmclinical@ozmosisresearch.ca or fax to 416-634-8333. Only after this has been submitted to Ozmosis can the patient receive investigational product(s)/treatment.

The protocol treatment is to be given within 5 working days of patient enrollment.

5. PRE-TREATMENT EVALUATION

Refer to *Appendix I: Schedule of Study Assessments and Evaluations*

5.1. Baseline Assessment

At baseline, a comprehensive clinical history and physical examination will be conducted. Clinical history will involve recording the date of CML diagnosis, phase at presentation, Sokal and ELTS (EUTOS Long-Term Survival) risk score (if available), and any additional chromosomal abnormalities identified on the diagnostic karyotype. If NGS test was performed at the time of initial diagnosis, this result will be also captured. All prior treatments, including the type of tyrosine kinase inhibitor (TKI), dosage, treatment response, toxicity and any treatment interruptions lasting longer than two weeks, will also be documented.

Acquired ABL1 kinase domain mutations and additional chromosomal abnormalities occurring prior to enrollment will be recorded along with the corresponding dates, if available.

6. STUDY TREATMENT/ INTERVENTION

Refer to *Appendix I: Schedule of Study Assessments and Evaluations*

6.1. Treatment/Intervention

All eligible patients who provide consent will initiate treatment with ASC at 80 mg daily for up to 12 cycles. Each cycle consists of 28 days (i.e., 4 weeks).

Upon enrollment, somatic mutation profiling will be performed through the central lab at Toronto General Hospital for next-generation sequencing (NGS) test. Based on the results of this assessment, patients will be stratified into two groups; those **with** a high-risk mutation profile and those **without** a high-risk mutation profile. Standard NGS testing will be performed on peripheral blood (PB) samples. Risk stratification will be centrally assessed based on the presence of genetic mutations and additional high-risk cytogenetic abnormalities.

Patients with a high-risk somatic mutation profile will also initiate standard of care treatment with DAS in addition to ASC 80 mg daily on Cycle 2 Day 1. Patients will initiate SOC DAS treatment at a starting dose of 100 mg, as indicated in the product monograph. Patients will continue on ASC 80 mg daily (with or without DAS) for maximum 12 cycles of 28 days each (i.e. total of 48 weeks), with potential dose modifications based on the development of adverse events and its severity (refer to tables 2a). Monitoring of *BCR::ABL1* transcript levels by PCR will occur every three cycles using local PCR test per SOC.

The two treatment strategies are summarized below:

1. **Patients without a high-risk mutation profile** will receive ASC 80 mg daily.
2. **Patients with a high-risk mutation profile** will receive ASC 80 mg daily in combination with SOC DAS (i.e.,100 mg) daily.

Patients who experience serious adverse events (more than 2 episodes, at least possibly related to study drug) without any clinical response, require discontinuation of the treatment for more than 28 days, or withdraw consent, will be discontinued from the trial. Additionally, the treating investigator holds the authority to discontinue a patient from treatment at any time if they deem it is not in the patient's best interest to continue receiving treatment.

6.2. Study Drug Administration

Product	Dose	Route Of Administration	Schedule
ASC	80 mg	Oral (PO)	Daily

All patients will receive open label investigational product. ASC should be taken once daily approximately 24 hours apart and should not be taken with food. No food should be consumed for 2 hours before the dose is taken and no additional oral intake other than water should be consumed for at least one hour after the dose is taken. Patients should be instructed to swallow tablets whole with a full 8 oz. glass of water, and not to chew them. Vomited doses should not be repeated.

6.3. Packaging and Labelling

For this protocol, ASC will be supplied to participating sites as 40 mg film coated tablets. Tablets are supplied in blister pack (10 blisters/card, 6 cards/carton).

The study drug will be labeled consistent with the regulatory requirements and local site guidelines.

6.4. Storage and Stability

All medication must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s). The storage conditions for investigational product will be provided on the medication label.

Do not store ASC above 25^{o} C. Store in the original package to protect from moisture. Patients should ensure study drug is kept out of the reach and sight of children when storing at home.

6.5. Accountability and Destruction of Study Drug

The QI or designee at each participating site must maintain a careful record of the inventory of the study drug received using a drug accountability form. Study drug accountability records will be available for review by the study monitor, as applicable, according to the monitoring plan. The local site pharmacies will follow the appropriate GCP for the storage and dispensing of the medication to the study patient.

The study drug should not be used for any purpose outside the scope of this protocol, nor can it be transferred or licensed to any party not participating in the clinical study.

Upon completion or termination of the study, the Sponsor shall follow Novartis' instructions regarding the return or disposal of all unused study drug. The Sponsor shall be responsible for compliance with all laws and regulations applicable to any destruction or disposal of study drug at participating sites. The Sponsor will follow the instructions of Novartis in case Novartis determines that a recall of the study drug is required and in addition, the Sponsor will inform Novartis should the Sponsor determine that a recall of the study drug is required.

The Sponsor should ensure that the site has acceptable drug destruction policies in place. Documentation of study drug destruction should be maintained by the site, filed in the trial master file and provided to Ozmosis upon request.

6.6. Drug Supply and Ordering

Study drug for the trial will be provided by Novartis. Sites must request study drug by submitting an order form to the drug depot, copying Ozmosis, in order for the study drug to be shipped to the site pharmacy. The QI (or designee) will verify and acknowledge receipt of all study drug shipments by signing and returning all required forms.

6.7. Assessment of Subject Compliance

Compliance to study medication will be ascertained by use of patient diaries and pill counting. Patients will record the date, time and number of pills consumed in the diary on a daily basis. The QI or designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the CRF and drug accountability logs for verification with the reasons. The QI/designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients.

6.8. Misuse/Abuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All sites must report any misuse and abuse of ASC to Ozmosis, who will report this to Novartis.

6.9. Modifications to Dose or Schedule

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow the patient to continue the study treatment. The dose modifications for ASC are summarized in Table 2. Dose modifications for DAS should be managed per standard of care. The dose reductions indicated as “recommendations” are provided to assist investigators in the event the patient experiences toxicity. All dose modifications should be based on the worst preceding toxicity.

Re-escalation is permitted if a change in the patient’s individual benefit/risk assessment at the lower dose level is seen. Re-escalation will be allowed only once. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 2. Any dose changes must be recorded in the Dose Administration eCRF. A patient must be

discontinued from treatment with either ASC or DAS if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity (See Table 2). If a patient requires a dose interruption of > 28 days, then the patient must be discontinued from the study treatment. Patients who discontinue the study treatment for an adverse event suspected to be related to study drug or an abnormal laboratory value suspected to be related to study drug must be followed.

Table 2. Dose modifications for patients on ASC treatment

Severity (CTCAE v5.0)	Guidance
Neutropenia	
Grade 1 (ANC < LLN – 1.5 x 10^9/L)	Recommendation: Maintain dose level
Grade 2 (ANC < 1.5 – 1.0 x 10^9/L)	Recommendation: Maintain dose level
Grade 3 (ANC < 1.0 – 0.5 x 10^9/L)	Mandatory: Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: If resolved in ≤14 days: Maintain dose level If resolved in >14 days: Reduce dose 1 dose level
Grade 4 (ANC < 0.5 x 10^9/L)	Mandatory: Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: If resolved in ≤14 days: Maintain dose level If resolved in >14 days: Reduce dose 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Mandatory: Hold dose until resolved then reduce dose 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN – 75 x 10^9/L)	Recommendation: Maintain dose level
Grade 2 (PLT < 75 – 50 x 10^9/L)	Recommendation: Maintain dose level
Grade 3 (PLT < 50 – 25 x 10^9/L)	Mandatory: Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: If resolved in ≤14 days: Maintain dose level If resolved in >14 days: Reduce dose 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Mandatory: Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: If resolved in ≤14 days: Maintain dose level If resolved in >14 days: Reduce dose 1 dose level
Recurrence of all cytopenias	Recommendation: For recurrent Grade 3-4 cytopenias: If resolved to ≤ Grade 2 in ≤ 14 days, maintain dose level If resolved in >14 days, then reduce dose 1 dose level
Non-Hematologic Adverse Reactions	

Grade 1	Recommendation: Maintain dose level
Grade 2	Recommendation: Hold dose until resolved to ≤ Grade 1, then maintain dose level
Grade 3	Mandatory: Hold dose until resolved to ≤ Grade 1, then reduce dose 1 dose level
Grade 4	Mandatory: Permanently discontinue from treatment
Serum Creatinine (Renal Impairment)	
Grade 1 (>ULN - 1.5 x ULN)	Recommendation: Maintain dose level
Grade 2 (>1.5 - 3.0 x ULN)	Recommendation: Hold dose until resolved to ≤ Grade 1 or baseline, then maintain dose level
Grade 3 (>3.0 - 6.0 x ULN)	Mandatory: Permanently discontinue from treatment
Grade 4 (>6.0 x ULN)	Mandatory: Permanently discontinue from treatment
Isolated Total Bilirubin Elevation	
> ULN – 1.5 × ULN	Recommendation: Maintain dose level
> 1.5 – 3.0 × ULN	Recommendation: Omit dose; repeat LFTs within 48-72 hours, then monitor weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline: If resolved in ≤14 days: maintain dose. If >14 days: Reduce dose, 1 dose level
> 3.0 – 10.0 × ULN	Mandatory: Omit dose; repeat LFTs within 48-72 hours, then monitor weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline: If resolved in ≤ 14 days, then reduce dose 1 dose level If resolved in > 14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks
> 10.0 × ULN	Mandatory: Permanently discontinue patient from treatment; monitor LFTs weekly (or more frequently if clinically indicated) until return to baseline or stabilization over 4 weeks
Isolated AST/ALT Elevation	
> ULN – 3.0 × ULN	Recommendation: Maintain dose level
> 3.0 – 5.0 × ULN	Recommendation: Maintain dose level. Repeat LFTs as soon as possible, ideally within 48–72h; if abnormal values are confirmed upon the repeat test, monitor LFTs weekly (or more frequently if clinically indicated) until ≤ 3.0 × ULN
> 5.0 – 10.0 × ULN	Mandatory: Omit dose. Repeat LFTs as soon as possible, ideally within 48–72h. Monitor LFTs weekly

	or more frequently if clinically indicated, until resolved to ≤ 3.0 × ULN. Then: If resolved in ≤ 14 days, resume dosing at prior dose level If resolved in > 14 days, resume with 1 dose level reduction
> 10.0 – 20.0 × ULN	Mandatory: Omit dose. Repeat LFTs as soon as possible, ideally within 48–72h. Monitor LFTs weekly or frequently if clinically indicated, until ≤ resolved to ≤ 3.0 × ULN. Then resume with 1 dose level reduction
> 20.0 × ULN	Mandatory: Permanently discontinue study treatment
Elevated baseline (> Baseline – 3 × Baseline AND < 5 × ULN)	Maintain dose level
Elevated baseline (> 3 × Baseline AND > 5 × ULN, duration < 2 weeks)	Mandatory: Maintain dose level. Repeat LFTs as soon as possible, preferably within 48–72 hours; if abnormal values are confirmed, monitor LFTs weekly or more frequently until resolved to ≤ ULN or baseline. Resume with same dose once resolved.
Elevated baseline (> 3 × Baseline AND > 5 × ULN, duration > 2 weeks)	Mandatory: Omit dose. Repeat LFTs as soon as possible, preferably within 48–72 hours; if abnormal values are confirmed, monitor LFTs weekly or more frequently until resolved to ≤ ULN or baseline. Resume with same dose once resolved.
Elevated baseline (> 5 × Baseline AND > 8 × ULN, any duration)	Mandatory: Omit dose. Repeat LFTs as soon as possible, preferably within 48–72 hours; if abnormal values are confirmed, monitor LFTs weekly or more frequently until resolved to ≤ ULN or baseline. If resolved, resume with 1 dose level reduction
> 20 × ULN	Permanently discontinue study treatment.
Combined elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis For patients with elevated baseline AST or ALT or total bilirubin value	Mandatory: Interrupt treatment and adjudicate for drug include liver injury (DILI). Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Mandatory: If causality assessment indicates DILI is probable, permanently discontinue patient from study treatment

AST or ALT > 3 x baseline OR [> 8.0 x ULN], whichever is lower, combined with total bilirubin > 2x baseline AND >2.0 x ULN **Note: For patients with Gilbert's syndrome, at least 2-fold increase in direct bilirubin	If not DILI: Treat the identified cause according to institutional guidelines. Once resolved, reduce by one dose level if cause is treatment related.
Asymptomatic amylase/lipase elevation	
Grade 1 (> ULN – 1.5 × ULN)	Recommendation: Maintain dose level; monitor 2x/week
Grade 2 (> 1.5 – 5.0 × ULN)	Recommendation: Maintain dose level; monitor 2x/week
Grade 3 (> 5.0 × ULN)	Mandatory: Hold dose until resolved to Grade ≤ 1 (1.5 × ULN) or baseline; If resolved in ≤7 days: Reduce dose 1 dose level If resolved in >7 days: Discontinue treatment and obtain appropriate imaging (i.e., MRI, CT scan or ultrasound)
Grade 4 (> 5.0 × ULN with symptoms)	Mandatory: Permanently discontinue study treatment and obtain appropriate imaging
Hypertension	
Grade 2 (Systolic 140-159 mmHg or Diastolic 90-99 mmgHg)	Recommendation: Maintain dose level. Initiate antihypertensive drug/increase the dose of existing antihypertensive drug or change treatment plan as per the Investigator's assessment
Grade 3 (Systolic ≥160 mmHg or Diastolic ≥100 mmHg)	Mandatory: Omit dose until resolved to ≤ Grade 1/baseline; then reduce dose, 1 dose level. Initiate antihypertensive drug/increase the dose of existing antihypertensive drug or change treatment plan as per the Investigator's assessment
Grade 4	Mandatory: Permanently discontinue from study treatment
Pancreatitis	
Grade 2 (enzyme elevations with radiologic findings for pancreatitis as per CTCAE v5.0. For isolated increased enzymes please see table for asymptomatic amylase and/or lipase elevation)	Mandatory: If radiologic pancreatitis, hold treatment until revocery of the radiologic findings. If treatment delay is ≤ 21 days, then reduce dose by 1 dose level. If treatment delay is > 21 days, discontinue treatment and keep monitoring with appropriate imaging (i.e., MRI, CT scan or ultrasound)
Grade ≥3	Mandatory: Permanently discontinue study treatment and obtain appropriate imaging

Cardiac Adverse Events	
LVEF < 45%	Recommended: For Grade 2 (asymptomatic, resting LVEF < 50 - 40%), close monitoring with a follow-up ECHO within 4 weeks is recommended. Mandatory: For Grade 3 events (symptomatic HF responsive to intervention; LVEF < 40 - 20%) follow guidance for cardiac "other" described below. For Grade 4 (refractory HF or poorly controlled; LVEF < 20%) Permanently discontinue patient from study drug treatment
QTcF prolongation	Mandatory: If QTcF >500 msec or QTcF prolongation >60 msec from baseline is observed at any point during study treatment, and confirmed, the below guidance must be followed: 1. Assess the quality of the ECG recording and the QT value and repeat if needed 2. Interrupt study treatment until confirmed resolution of QTcF and as per dose reduction guidelines for non-hematological AEs. 3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, replace it and correct abnormalities before resuming study drug treatment. 4. Review concomitant medication use for other causes for QT prolongation (refer to qtdrugs.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation (e.g., concomitant use of CYP3A4 inhibitors, if the study drug is a CYP3A4 substrate) 5. Check study drug dosing schedule and treatment compliance 6. Increased ECG safety monitoring is recommended during or in-between subsequent visits.
Cardiac "other"	Grade 2: Omit dose until ≤ Grade 1, then Reduce dose, 1 dose level; Grade ≥3: Permanently discontinue & imaging
Pleural or Pericardial Effusion	
All grades	Mandatory: Both ASC and DAS should be held. An echocardiogram can be performed to assess pulmonary hypertension, if suspected. Once the

	effusion has fully resolved, ASC can be resumed, with chest X-ray assessments. DAS should be permanently discontinued if recurs
Diarrhea	
Grade 1	Recommendation: Maintain dose level; start anti-diarrhea medication
Grade 2	Recommendation: Hold dose until resolved (initiate anti-diarrhea treatment) to ≤ Grade 1, then maintain dose level. If diarrhea returns as ≥ Grade 2, then hold dose until resolved to ≤ Grade 1, then reduce dose by 1 dose level
Grade 3	Recommendation: Hold dose, initiate anti-diarrhea treatment and discontinue patient from study drug treatment
Grade 4	Mandatory: Initiate anti- diarrhea treatment and permanently discontinue patient from study drug treatment
Skin/Subcutaneous Disorders	
Grade 1	Recommendation: Maintain dose level. Consider initiating skin toxicity therapy (e.g., antihistamines, topical or low-dose systemic corticosteroids)
Grade 2	Recommendation: Maintain dose level. Intensify/initiate appropriate skin toxicity therapy
Grade 3, despite skin toxicity therapy	Recommendation: Hold dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, reduce dose by 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment
Grade 4, despite skin toxicity therapy	Mandatory: Permanently discontinue from study treatment
Fatigue / Asthenia	
Grade 1–2	Recommendation: Maintain dose level
Grade 3	Recommendation: Omit dose until ≤ Grade 1; if ≤7 days: maintain dose; if >7 days: Reduce dose, 1 dose level
Hypersensitivity Reactions:	
Grade 1–2	Recommendation: Interrupt until symptoms resolve to Grade ≤1 Initiate appropriate medical management (e.g., antihistamines ± corticosteroids) Resume at the same or reduced dose, based on clinical judgment
Grade 3	Recommendation: Interrupt immediately

	Initiate appropriate medical treatment (e.g., systemic corticosteroids, supportive care) Rechallenge: May resume at a reduced dose only if symptoms fully resolve and the benefit–risk assessment supports rechallenge Permanent discontinuation should be considered if reaction recurs
Other AEs	
Grade 1–2	Recommendation: Maintain dose level
Grade 3	Mandatory: Hold dose; if resolved ≤ 28 days: Resume dosing at 1 dose level reduction
Grade 4	Mandatory: Omit dose until ≤ Grade 1; if ≤7 days: maintain dose; if >7 days: Reduce dose, 1 dose level

For patients receiving combination therapy of ASC and DAS, if treatment is temporarily discontinued, resume ASC alone for 7–14 days, once the criteria for resumption are met. If no recurrence occurs, resume DAS. If ASC and/or DAS are held for more than 28 days, therapy will be permanently discontinued.

Follow-up for toxicities in patients whose treatment is permanently discontinued due to a study drug related adverse event or clinically significant laboratory value, should be performed once a week or every 2 weeks for 4 weeks, depending on severity. Follow up should be continued until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such should be consulted as deemed necessary.

Table 3. Dose Reduction Steps

Drug	Starting Dose (Level 0)	Dose Level -1	Dose Level -2	Minimum Allowed Dose	Tablet Dispensed
ASC	80 mg QD	40 mg QD	*Not allowed*	40 mg/day	40 mg tablets

6.10. Concomitant Medications

Details of any concomitant medications (including herbal or alternative medicines) taken by the patient at study entry and during protocol therapy must be recorded on the appropriate eCRFs. See Table 4 below for a list of concomitant medications and their associated guidance/restrictions.

Table 4. Concomitant medication guide

Drug/Class	Guidance / Restrictions	Notes / Monitoring
Anti-emetics	Allowed; initiate prophylactically only after nausea/vomiting	Prefer drugs without QT prolongation; monitor for TdP risk
Hormonal contraceptives	Allowed	Standard contraceptive guidance applies
Anticoagulants / Anti-platelet agents	Allowed under Investigator discretion	Warfarin: monitor closely due to CYP2C9 interactions; Anti-PLT pro-drugs: careful monitoring; DTIs and Factor Xa inhibitors allowed; LMWH acceptable alternative
Acid-reducing agents	Allowed	No effect on ASC absorption
CYP3A4/5 substrates (narrow therapeutic index)	Use with caution	Dose adjustment per prescribing information
CYP2C9 substrates (narrow therapeutic index)	Use with caution	Monitor for interactions, adjust dose as needed
Strong CYP3A4 inducers	Not allowed	May reduce ASC exposure
OATP1B/BCRP substrates	Use with caution	Adjust dose or avoid co-administration; e.g., statins (rosuvastatin, simvastatin, atorvastatin, pitavastatin)
Drugs with Known/Possible/Conditional TdP risk	Avoid if possible	If necessary, continue under close ECG monitoring
Investigator-selected TKI	Follow local label	Adhere to concomitant therapy restrictions
Bisphosphonates	Allowed	No restrictions

7. EVALUATION DURING and AFTER INTERVENTION

Appendix I: Schedule of Study Assessments and Evaluations

7.1 Efficacy Assessments

Complete Hematologic Response (CHR):
CHR is defined as meeting **all** of the following criteria present for $\geq$ 4 weeks:

- WBC count < 10 × 10^9/L or within the upper limit of normal (ULN) per local laboratory
- No immature granulocytes present in peripheral blood
- Basophils < 5%
- Platelet count < 450 × 10^9/L

- Non-palpable spleen

Molecular Response:
Molecular response will be assessed in all patients. Levels of *BCR::ABL1* transcripts will be determined by real-time quantitative polymerase chain reaction (RQ-PCR) on peripheral blood samples, analyzed at each treating center.

Results will be expressed as:
- Log reduction in *BCR::ABL1* transcript levels from standardized baseline values, or
- Percent ratio of *BCR::ABL1* to control gene (*ABL1*) transcripts, converted to the International Scale (IS).

Definitions:
- **Major Molecular Response (MMR):** *BCR::ABL1* (IS) ≤ 0.1%
- **MR4:** *BCR::ABL1* (IS) ≤ 0.01%
- **MR4.5:** *BCR::ABL1* (IS) ≤ 0.0032%
- **MR5:** *BCR::ABL1* (IS) ≤ 0.001%

Loss of MMR
Defined as:
- Increase of *BCR::ABL1/ABL1* > 0.1% (IS), **and**
- ≥ 5-fold rise in *BCR::ABL1* from the lowest value achieved on study treatment,
- Confirmed by repeat testing of the same sample, and verified by a subsequent sample within 4–6 weeks.

Loss of MMR can also be confirmed if associated with:
- Loss of CHR, or
- Loss of complete cytogenetic response (CCyR), or
- Progression to accelerated phase, blast phase, or CML-related death.

Progression to Advanced Disease
Progression is defined as development of:
- Accelerated phase: presence of 15–29% blasts in bone marrow or peripheral blood, ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate, ≥20% basophils in the peripheral blood
- Blast phase (BP): ≥30% blasts in bone marrow or peripheral blood, or extramedullary blast proliferation (proven by biopsy)
- Acquisition of new additional cytogenetic mutations

Any value of AP or BC within the first 4 weeks of study treatment is not considered as progression to AP/BC unless the patient discontinues study treatment due to progression or unsatisfactory therapeutic effect within the first 8 weeks.

Treatment Failure
Treatment failure is defined as any of the following:

- Failure to achieve CHR within 3 months of treatment initiation
- BCR-ABLI transcript level > 10% IS at 3 months if confirmed within the next 1-3 months
- BCR-ABLI transcript level > 10% IS at 6 months
- BCR-ABLI transcript level > 1% IS at 12 months
- Evidence of disease progression (i.e. increased blasts above 15% in the marrow or peripheral blood)
- Acquisition of new additional cytogenetic abnormalities
- Acquisition of ABL KM mutation

7.2 Optional Sub-Study

All patients who agree to participate in this study, will also be presented with the option to have their blood samples stored for future research. Study samples will be sent to the Advanced Molecular Diagnostics Laboratory in Toronto, Canada for genetic testing for the purpose of the main study. If is the patient consents to the long term storage and use of samples for future research, they will be stored at this location for up to 10 years. If the patient declines consent to the optional study, the samples will be destroyed following the genetic testing. Access to samples in long term storage (for patents who consented) will be restricted to representatives delegated by the PI. Samples will be de-identified by using a unique patient number. Refer to laboratory manual for details or correlative sample storage.

8. DISCONTINUATION OF PROTOCOL

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. In addition, the QI may decide to withdraw the patient from the study if he/she feels that it is in the best interest of the patient's health and safety. Patients who discontinue study treatment should undergo an end of treatment (EOT) visit. For patients who discontinue treatment for reasons other than death, lost to follow-up, or withdrawal of consent, the 30-day safety

follow-up visit should be performed. Patients who discontinue the study treatment due to an adverse event or abnormal laboratory value suspected to be related to study drug, must be followed until resolution. Note that the EOT visit is not required to be performed in patients who complete the treatment duration period (i.e., perform the C12D28 visit). This is because the C12D28 visit will be the date of the last dose administered, and assessments performed on this day will not need to be repeated within 7 days. The EOT visit will only be applicable for patients who come off treatment due to progression, treatment failure or intolerance.

Patients who experience serious adverse events (more than 2 episodes, at least possibly related to study drug) without any clinical response, require discontinuation of the treatment for more than 28 days, or withdraw consent, will be discontinued from the trial. Additionally, the treating investigator holds the authority to discontinue a patient from treatment at any time if they deem it is not in the patient's best interest to continue receiving treatment.

Patients may also be discontinued from the study treatment if any of the following occurs:

- Disease progression
- Discovery of patient ineligibility
- Errors in treatment compliance [study treatment, other prescribed or non-prescribed medications]
- Missed/unscheduled/off schedule/incomplete/incorrect assessments
- Major protocol deviation
- Pregnancy during treatment phase
- Intercurrent illness that interferes with study assessments
- Other treatments become available
- Any other protocol deviation that results in a significant risk to the patient's safety

8.1. Termination of Protocol

The study can be terminated at any time for any reason by the sponsor. Should this be necessary, the patients should be contacted as soon as possible and instructed to stop taking study medication. The end of treatment visit should be scheduled and the same assessments should be performed. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing REBs of the early termination of the trial. As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

8.1.2 Criteria for Early Permanent Discontinuation of Protocol Treatment

Reasons for permanent discontinuation of protocol treatment due to adverse events are outlined under the section "Modifications to Dose or Schedule." Patients may continue therapy for up to 48 weeks as long as they derive clinical benefit and no adverse event warrants permanent discontinuation. Upon completion of the clinical trial, patients will transition to a commercially available TKI. It would be the responsibility of the study investigator to assess the best available treatment option for the patients.

9. SAFETY AND REPORTING REQUIREMENTS

This study will be conducted in accordance with Health Canada regulatory requirements and ICH Good Clinical Practice Guidelines. Adverse Events (AEs) and Serious Adverse Events (SAEs) data will be reported and collected.

9.1. Adverse Event Definitions

An **adverse event** (AE) is defined as any untoward medical occurrence in a clinical investigation patient who is administered a drug or biologic (medicinal product) or using a medical device; the event does not necessarily have to have a causal relationship with this treatment or usage. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Each AE is to be classified by the investigator as serious or non-serious.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after administration of the study product unless they reoccur after the patient has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

A laboratory test abnormality considered clinically relevant (e.g. causing the patient to withdraw from the study, requiring treatment or causing apparent clinical manifestations) or judged relevant by the QI should be reported as an AE.

9.2. Adverse Event Documentation

AEs will use the descriptions and grading scales found in the revised NCI CTCAE. This study will utilize the CTCAE Version 5.0 for AE reporting.

All AEs must be recorded in the eCRFs. Documentation must be supported by an entry in the patient’s file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the QI, action taken and outcome.

9.3. Attribution Definitions

For all AEs, relationship to investigational product will be reported on the appropriate AE CRF page. The PI must judge whether the investigational product caused or contributed to the AE in which case it is considered to be an adverse drug reaction (ADR), and report it as either:

Related (definitely, probably or possibly): there is a reasonable possibility that the investigational product caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for the determination of relatedness:

- There is a plausible time sequence between onset of the AE and investigational product administration;
- There is a plausible biological mechanism through which investigational product may have caused or contributed to the AE.

Not related (unrelated, unlikely related): It is highly unlikely or impossible that the investigational product caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for a determination of not related:

- Another cause of the AE is evident and most plausible; the temporal sequence is inconsistent between the onset of the AE and investigational product administration; a causal relationship is considered biologically implausible.

9.4. Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly / birth defect
- Is an important medical event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (example: intensive treatment in an emergency room or at home for bronchospasm, convulsions that do not result in hospitalization). Medical and scientific judgment should be exercised in deciding whether some events should be considered as serious because their quick reporting to the Sponsor may be of interest for the overall conduct of the study.

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an adverse event in which the patient was at risk of death at the time of the event. It does not refer to an adverse event that hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions are met:

- The admission results in a hospital stay of less than 12 hours.

  OR

- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study or for prophylactic insertion of a gastric feeding tube).

  OR

- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfil the criteria of ‘medically important’ and as such may be reportable as an SAE dependant on clinical judgement. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition.

Any death (regardless of cause) that occurs from the time of administration of the first dose of study therapy until 30 days after the final administration of the investigational product, and any death occurring after this time that is judged at least possibly related to prior treatment with the investigational product, will be promptly reported.

An AE is **unexpected** when the nature or severity of the AE is not consistent with the applicable product information (i.e. investigator’s brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). An AE is considered to be associated with the use of the drug if the attribution is classified as “possible”, “probable” or “very likely”.

9.5. Adverse Event Reporting Criteria

AEs are to be recorded within the CRF. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, grade, action taken with respect to the investigational product, corrective treatment

or therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was related to the investigational product.

The severity of all AEs will be graded according to the NCI CTCAE, version 5.0. For each event, the highest severity grade attained since the last assessment period will be reported.

9.6. Adverse Event Reporting Period

The AE reporting period begins at the time the patient receives their first dose of study treatment. All AEs and SAEs must be followed until resolution or 30 days following the last dose of study treatment, whichever comes first.

Patients withdrawn from the study due to an AE will be followed until the AE has resolved. In the case of an SAE, the patient will be followed until clinical recovery or until progression has been stabilized or judged to be chronic. After discontinuation from protocol treatment, all patients will be followed for any ongoing or late toxicities. Patients will be seen 30 ± 7 days after discontinuing treatment. Safety Follow up procedures will be completed as indicated in the Study Calendar.

9.7. Serious Adverse Event Reporting to Ozmosis

All SAEs defined as per section **Error! Reference source not found.**3 must be recorded on case report forms. In addition, they must be reported to Ozmosis according to the following instructions:

1. Within 24 hours of becoming aware of the event, report initial information (on trial specific SAE report form) by fax or e-mail to:

   Ozmosis Research Inc.
   Fax: 416-634-8333
   E-mail: ozmsafety@ozmosisresearch.ca

   - The initial information should always contain:
     - Name of reporter/Site Investigator,
     - Patient identification,
     - AE Term and grade,
     - Investigational product dose and start/stop dates

2. On the next working day *if the initial report in step #1 did not contain complete information*: Fax completed trial-specific SAE form
3. Follow-up SAE reports should be submitted to Ozmosis as soon as possible.

All SAEs must be followed until resolved, become chronic, or stable unless the patient is lost to follow up. Resolution status of such an event should be documented on the eCRF.

9.8. Exceptions and Non-Reportable SAEs

Progressive disease and death due to progressive disease will not be reportable as an SAE in this study. Progression of the underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer. Clinical symptoms of progression may be reported as an AE if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. If there is any uncertainty of an AE being due only to cancer it should be reported as an AE or SAE.

Elective procedures requiring hospitalization will not be considered SAE's if they were pre-planned prior to signing consent; however, other events may occur during this hospitalization that may be considered serious or non-serious adverse events and will need to be captured according to the protocol SAE reporting period if hospitalization is prolonged.

9.9. Serious Adverse Event Reporting to Health Canada

Ozmosis, acting on behalf of Sponsor, will be responsible for notifying Health Canada in an expedited manner of adverse events which are considered *serious* and *unexpected* and *related* to the protocol treatment (or for which a causal relationship with the protocol treatment cannot be ruled out). Follow-up of SAEs as documented and submitted by the clinical site on the Ozmosis. SAE form will be forwarded to Health Canada by Ozmosis, where applicable.

9.10. Reporting SAEs to Local Research Ethics Boards

SAEs occurring within a site should also be reported to local ethics boards according to their local policies.

Ozmosis will notify all Principal Investigators of all SAEs that are reportable to regulatory authorities from this trial or from other clinical trials as reported to the Sponsor. Principal Investigators (or their designee) must notify their ethics boards and file the report with their Investigator Site File.

Documentation that SAEs have been reported to ethics boards must be provided by the site to Ozmosis, and kept on file at the site and Ozmosis.

9.11. Reporting of Pregnancy

Pregnancies occurring in study patients/sexual partner(s) will be treated procedurally as SAEs. Pregnancies occurring in study patients or their sexual partner(s) after investigational product treatment should be reported separately on the Pregnancy Report Form to Ozmosis and the patient must discontinue the trial medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient has discontinued from the study.

Pregnancy in itself, occurring in female patients, and female partners of male patients is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication.

The QIs are required to report to Ozmosis any pregnancy occurring in female patients, and female partners of male patients. Women of childbearing potential will be instructed to contact the investigator or study staff immediately if they suspect they might be pregnant (e.g. missed or late menstrual period) at any time during study participation.

The investigator must immediately notify Ozmosis if a study subject becomes pregnant and discontinue trial. Any drug exposures during pregnancy must immediately be reported to Ozmosis. Ozmosis will then report this to Novartis within 15 days of receipt.

9.12. Ozmosis Reporting Responsibility to Pharmaceutical Company

Ozmosis, acting on behalf of the Sponsor, will notify Novartis of all SAEs, any misuse/abuse of ASC, or any ASC exposure during pregnancy within 15 days of receipt of reports from the sites.

10. STUDY OUTCOMES

10.1. Primary Outcome

The primary outcome will be the proportion of patients achieving MMR, defined as a 3-log reduction or deeper (0.1% International Scale), after 24 weeks (6 cycles) of treatment with ASC as a second-line therapy.

10.2. Secondary Outcomes

The secondary outcomes will be:

1. The proportion of patients achieving MMR, defined as a 3-log reduction or deeper (0.1% International Scale), after 12 and 48 weeks (3 and 12 cycles) of treatment with ASC as a second-line therapy
2. The proportion of patients achieving MMR, defined as a 3-log reduction or deeper (0.1% International Scale), after 12, 24 and 48 weeks (3, 6 and 12 cycles) of second-line therapy treatment.
3. The safety of ASC +/- DAS when used as a second-line therapy as assessed by the:
    A. Adverse Events (AEs):

1. Incidence, severity (NCI CTCAE v5.0), and relationship to study drug
2. Tabulation by system organ class (SOC) and preferred term (PT)
3. Specific analyses will include:
    i. Incidence of Grade ⩾3 AEs
    ii. Incidence of Serious AEs (SAEs)
    iii. AEs leading to discontinuation, dose reduction, or interruption
    iv. AEs of special interest: pleural effusion, pulmonary hypertension, pancreatitis, cardiac events, QT prolongation

B. Laboratory Parameters:

1. Shift tables (baseline to worst post-baseline grade)
2. Descriptive statistics for hematology, serum chemistry, and lipase parameters
3. Incidence of CTCAE Grade 3/4 abnormalities

C. Vital Signs and ECG:

1. Descriptive summary of changes from baseline
2. Incidence of QTcF >500 ms or increase >60 ms

D. Physical Examination and ECOG Status:

1. Summary of changes

E. Dose Intensity and Modifications:

1. Percentage of planned dose received (dose intensity)
2. Frequency and reasons for dose reduction, interruption or discontinuations

10.3. Definitions

Evaluable for adverse events. All patients will be evaluable for adverse event evaluation from the time of their first dose.

Evaluable for response. All patients who have their CML evaluated after 3, 6 and / or 12 cycles, will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of their treatment period).

10.4. Measuring Response

Peripheral blood samples for RQ-PCR will be collected and processed locally to assess molecular response. Molecular response will be assessed in all participants at predefined time points (weeks 12, 24, and 48 of treatment).

The response criteria used in this study are those previously defined: A major molecular response (MMR) is defined as a BCR/ABL transcript level 0.1%IS, and a molecular response with 2 log reduction and 4.5 log reduction or deeper will be defined as a BCR/ABL transcript level of 1%IS or 0.0032%IS, respectively.

Time to treatment failure is defined as the interval between the initiation of treatment and the occurrence of events that indicated possible treatment failure, including primary hematologic resistance, cytogenetic resistance, loss of MR2, development of tyrosine kinase domain mutation, clonal evolution and progression to accelerated phase, or blast crisis. Time to progression free survival (PFS) is defined as the interval between initiation of treatment and confirmed progression to accelerated AP or BC or death from any cause, whereas OS is calculated from initiation of treatment until the date of death from any cause or until last follow-up. Event will be captured including discontinuation of treatment due to adverse events, treatment failure (primary hematologic resistance, cytogenetic resistance, loss of MR2, development of tyrosine kinase domain mutation, clonal evolution and progression to AP/BC.

To further elucidate the dynamic nature of somatic mutations in response to therapeutic interventions, NGS-based somatic mutation profiling will be repeated at the end of the treatment. This follow-up assessment is essential for evaluating mutational changes or evolutionary dynamics that may occur during the treatment period, such as the emergence of new mutations, clonal expansion, or reduction in variant allele frequencies. By comparing the baseline mutational profile obtained at enrollment with the end-of-treatment results, we can correlate these alterations with key clinical outcomes, including molecular response rates, disease progression, or treatment resistance. This exploratory analysis will provide valuable insights into the mechanisms underlying therapeutic efficacy or failure of ASC-based second line therapy, potentially informing future risk stratification models and personalized treatment strategies, while ensuring the study's preliminary findings contribute to a deeper understanding of CML biology without imposing undue burden on participants.

11. STATISTICAL ANALYSIS

The final analysis will be performed once all participants have either completed at least 48 weeks of treatment or discontinued study treatment prior to Week 48. Data from all participating centers will be pooled to ensure an adequate sample size for analysis.

Demographic and baseline disease characteristics will be summarized descriptively. Categorical variables will be presented as frequencies and percentages, and continuous variables as mean, SD, median, minimum, and maximum; for selected parameters, the 25th and 75th percentiles will also be provided.

The number of participants with dose modifications (reductions, interruptions, or permanent discontinuations) and the corresponding reasons will be summarized. All dosing data will be listed. Categorical variables will be summarized as frequencies and percentages, while continuous variables will be summarized using mean, SD, median, 25th and 75th percentiles, minimum, and maximum.

The primary endpoint is the binary outcome (Yes/No) of whether a participant achieves MMR at Week 24. The proportion of patients achieving MMR and corresponding 95% CIs will be estimated. Participants who discontinue treatment for any reason (e.g., intolerance, death) or who meet treatment failure criteria prior to the scheduled assessment will be counted as not achieving MMR at that time point.

Molecular response (MR2, MMR and MR2.5) as the binary outcome (Yes/No) at 12, 24, and 48 weeks will also be assessed. The proportion of patients achieving MMR and corresponding 95% CIs will be estimated.

There are no planned interim analyses for this study.

11.1. General Statistical Considerations

Demographic and baseline characteristics (including, but not limited to, age, sex, mutation profile, and baseline ECOG Performance Status) will be summarized by treatment group for all patients. Continuous variables will be summarized using descriptive statistics (i.e., number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized by frequency and its corresponding percentage. Graphical summaries of the data may also be presented.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. Additional exploratory analyses of the data will be conducted as deemed appropriate.

11.2. Sample Size Calculation

The calculation assumes that 40% of enrolled patients will have a somatic mutation profile, while 60% will not. The primary endpoint is the MMR rate, with the null hypothesis

positing an MMR rate of 40% for the non-mutated group and 20% for the mutated group, and the alternative hypothesis expecting an MMR rate of 60% for the non-mutated group and 55% for the mutated group. A one-sided exact binomial test will be used to evaluate the primary endpoint in each arm, with $\alpha = 0.01$, and a statistical power of 80% . The calculation indicates that 45 evaluable patients are required to detect these differences.

11.3. Evaluation of Study Endpoints

All endpoint analyses will be performed using the intention to treat (ITT) population, unless otherwise specified. This will consist of all enrolled patients, with patients grouped according to their assigned treatment or pre-specified characteristics.

11.3.1 Evaluation of the Primary Endpoint

The first primary outcome, which is the proportion of evaluable patients who achieve MMR after 6 cycles (24 weeks) will be tested using a one-sided, one-sample test of proportions.

11.3.1 Evaluation of the Secondary Endpoints

The proportion of the evaluable patients achieving MMR, MR2, and MR4.5 will be calculated at 3, 6 and 12 cycles time points with intent-to-treat basis. The cumulative incidences of MMR, MR2 and MR4.5 will be estimated using the cumulative incidence method considering the competing risks of treatment discontinuation and death. The probabilities of freedom from treatment failure, event free (EFS), progression-free (PFS), and OS will be calculated using the Kaplan-Meier method. The start of follow-up and censor date of these outcomes are clarified in Table 5.

Table 5. Summary of Secondary Endpoints

Endpoint	Start of Follow-Up	Event Definition	Censoring
EFS (Event-Free Survival)	Cycle 1 Day 1	Progression to AP/BC, loss of MMR (confirmed), or death from any cause	Last contact with confirmed MMR and no progression
PFS (Progression-Free Survival)	Cycle 1 Day 1	Progression to AP/BC or death from any cause	Last contact without progression
OS (Overall Survival)	Cycle 1 Day 1	Death from any cause	Last known alive date

- All time-to-event analyses use Kaplan-Meier estimation.
- Follow-up continues up to 48 weeks of treatment + 30-day safety follow-up, then long-term follow-up every 3 months until study closure or withdrawal.

- Censoring occurs at the last assessment date where the patient was known to be event-free/alive.

11.4. Final Analysis and Reporting

The final analysis will be conducted when the accrual target has been met, and all patients have completed their final study visit. Any deviation from the original statistical plan will be described in the final report.

12. STUDY SIGNIFICANCE

Despite significant advancements in the treatment of CML with TKIs, many patients do not respond adequately to first-line therapy.

According to the ASCEMBL trial results and follow-up analyses, ASC is effective in achieving an MMR rate of 57% following the completion of 3, 6, and 12 cycles of treatment when used as a second-line treatment. It has been hypothesized that when combined with DAS, patients can overcome the poor outcomes associated with frequently mutated somatic mutations. This novel, mutation-oriented approach could potentially offer a form of precision medicine for CML patients, tailoring treatments to their specific genetic profiles and improving overall treatment outcomes.

13. ETHICS

13.1. Informed Consent

Patient/Legally acceptable representative (LAR) consent must be obtained according to local site and/or ethics board requirements prior to any study-specific screening procedures. It will be the responsibility of the QI to obtain the necessary clearance, and to indicate in writing to Ozmosis that such clearance has been obtained, before the trial can commence at that site. Sample English consent forms for the trial will be provided. A copy of the initial full board ethics board approval and approved consent form must be sent to Ozmosis. The patient/LAR must sign consent prior to registration/enrollment.

13.2. Research Ethics Board (REB)

Each participating site will have on file with Ozmosis, a list indicating the composition of its ethics board consistent with regulatory guidelines. This list will be updated as appropriate.

For Canadian sites, a Health Canada REB Attestation Form must be completed and signed by the REB representative. Alternatively, an attestation may be included in the

signed local ethics approval document. This documentation must be received by Ozmosis before the site can be locally activated.

Initial approval: All study sites are required to obtain full board ethics approval of the protocol and consent form by the appropriate ethics board prior to commencement of the clinical trial at each site.

Continuing approval: Annual (or as required by the ethics board) re-approval may be required for as long as patients are being followed on protocol. It will be the Principal Investigator's responsibility to apply for and obtain the re-approval.

Amendment: Any amendments or modifications to the study protocol and/or ICF document, as issued by Ozmosis, must be submitted to and approved by Novartis. All protocol amendments will be confirmed in writing and submitted, as appropriate, for review by the ethics board and health authorities. Amendments will be reviewed and approved by applicable regulatory authorities prior to central implementation of the amendment, and by ethics boards prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial patients or when the change(s) involve(s) only logistical or administrative aspects of the trial.

Ethics board refusals: If an ethics board refuses to approve this protocol (or an amendment/revision to this protocol), Ozmosis must be notified immediately of the date of refusal and the reason(s) for the refusal. Notification will then be made to the regulatory authorities.

SAEs, safety updates and investigator brochure updates: During the course of the study SAEs, safety updates or investigator brochure updates may be sent to sites for reporting to their ethics board. If/when this occurs documentation of ethics board submission must be forwarded to Ozmosis.

14. RESPONSIBILITIES of the INVESTIGATOR

One QI will oversee the trial at each clinical site. The QI performs the study in accordance with this clinical trial protocol, ICH Guidelines for Good Clinical Practice and the applicable Health Canada regulations and local REB requirements.

The QI may appoint other individuals as he/she deems appropriate to assist in the study's conduct. All appointed designates will be listed and provided to Ozmosis. The appointed designates will be supervised by and under the QI's responsibility.

For ensuring compliance with the clinical trial protocol, ICH GCP and applicable regulatory requirements, the QI agrees to permit study monitoring/auditing by or on the behalf of Ozmosis and inspection by applicable regulatory authorities. The investigator

agrees to allow the auditors/inspectors to have direct access to his/her study records, including source data/documents.

15. DOCUMENTATION, RECORD ACCESS AND MAINTENANCE OF STUDY RECORDS

15.1. Documentation of Patient's Participation

A statement acknowledging the participation of a patient in this clinical trial must be documented in the patient's medical records along with the signed ICF.

15.2. Regulatory Requirements

The following documents are required:

- All Principal Investigators must complete and sign the Health Canada Qualified Investigator Undertaking form. The completed forms must be returned to Ozmosis prior to any drug shipment.
- Ozmosis will submit a completed Health Canada Clinical Trial Site Information Form to Health Canada after local activation of each participating Canadian site.
- All applicable regulatory documents as listed in the Site Activation Checklist provided by Ozmosis to the sites.
- A copy of the initial full board approval letter from the ethics board. Continuing approval (full board) will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purpose.

15.3. Patient Confidentiality and Access to Source Data/Documents

Any research information obtained about the patient in this study will be kept confidential. A patient will not be identified by name. The patient's name or any identifying information will not appear in any reports published as a result of this study.

However, information obtained from the patient's participation in the study may be disclosed with their consent to the health care providers for the purpose of obtaining appropriate medical care. The patient's medical records/charts, tests will be made available to Ozmosis, the Sponsor's partners, the Canadian regulatory authority Health Canada, the ethics boards and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A patient's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind

locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A patient may take away their permission to collect, use and share information about them at any time. If this situation occurs, the patient will not be able to remain in the study. No new information that identifies the patient will be gathered after that date. However, the information about the patient that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

15.4. Confidentiality of the Study

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the ethics board. The Principal Investigator shall permit the Sponsor, authorized agents of the Sponsor, CRO and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all source documents. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of the Sponsor.

15.5. Study Data at the End of Registration of Clinical Trial

Prior to the first patient being enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered (e.g. clinicaltrials.gov) appropriately to remain eligible for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE).

15.6. Data Reporting

The data will be collected in electronic CRFs using a Medidata database.

Please see the study specific eCRF Completion Guidelines for additional details. The timelines and details for completion of eCRFs are included in these guidelines.

15.7. Maintenance of Study Records

To enable evaluations and/or audits from regulatory authorities, Ozmosis or the Sponsor, the Principal Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eCRFs and hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of treatment disposition. The PI should retain these records for 15 years after study close-out as required by Canadian regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the PI relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another QI, another institution, or to the Sponsor. The PI must obtain the Sponsor's written permission before disposing of any records.

16. QUALITY ASSURANCE AND QUALITY CONTROL

As per the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the Sponsor will be responsible for implementing and maintaining quality assurance and quality control systems.

16.1. Monitoring/Auditing

Ozmosis will organize monitoring to be conducted as per the Monitoring Plan.

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Products and Food Branch Inspectorate. Other audits may be conducted by the Sponsor, Novartis, Ozmosis, and/or other regulatory authorities.

17. ADMINISTRATIVE PROCEDURES

17.1. Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments authorized by the Sponsor. All protocol amendments will be approved by the ethics board prior to implementation. QIs must not implement any deviation from, or change to the protocol, except where it is necessary to eliminate an immediate hazard to trial patient or when the change(s) involves only logistical or administrative aspects of the trial.

An amendment may require a change to the ICF. The investigator must receive REB approval/favorable opinion of the revised ICF before implementing the change.

17.2. Protocol Deviations and Violations

All violations or deviations are to be reported to the site's ethics board (as per ethics board guidelines). All ethics board correspondence is to be forwarded to Ozmosis. The site must notify Ozmosis and/or the Sponsor immediately of any protocol violations.

17.3. Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the trial for any reason but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the QIs must contact all participating patients immediately after notification is provided by the Sponsor. Standard therapy and follow-up for patients will be assured and, where required by the applicable regulatory requirement(s), the relevant regulatory authority(ies) will be informed.

The ethics board will be informed promptly by the site and will be provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

18. STUDY ORGANIZATION

18.1. Steering Committee

The Steering Committee is responsible for the trial's overall conduct, including the design, execution, analyses and reporting. In addition, the Steering Committee is also responsible for the assignment of responsibilities to other study committees. The Steering Committee will hold the primary responsibility for the publication of the study results. This Committee will convene on a regular basis by teleconference or face-to-face meetings at least every six months to address policy issues, to monitor study progress, execution and management and to review the reports from the DSMC. A list of the Steering Committee members is maintained by Ozmosis.

18.2. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) has been established. The DSMB will comprise of clinical trial experts in hematology and clinical trial methodology, independent of the study. A list of the DSMB members can be found in the DSMB charter.

The DSMB will monitor the safety aspects of the trial including review of all SAEs and accumulating safety data during the Safety Review Meeting as per the timelines in the DSMB Charter. Additional meetings may be scheduled as necessary. Please refer to the DSMB Charter.

19. SCIENTIFIC REPORTING and PUBLICATION

This clinical trial protocol was developed by the principal investigators with the assistance of Ozmosis.

The Steering Committee is responsible for the scientific reporting, publishing and/or presentation of the study results. Authorship will be determined by the Steering Committee and guided by the extent of participation in the protocol's development, accrual of patients to the study, involvement in the study analysis and the final manuscript drafting. Results of the study will be disseminated through publications and presentations at international meetings. Any other publication or presentation related to the study and the results by any investigator or patient must receive prior approval from the Steering Committee. No other publication or presentation is permitted before the primary publication or presentation by the Steering Committee.

The information developed during the conduct of this clinical study is considered confidential.

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Appendix I: Schedule of Study Assessments and Evaluations

	Screening	**Treatment**										**End of Treatment and Follow Up**	
Visit Name	**Screening**	C1 D1	C1 D15	C2 D1	C2 D8[12]	C2 D15[12]	C3 D1	C4 D1	C7 D1	C10 D1	C12 D28	EOT Visit[13]	30 Day Safety FU
Window	-21 days	+/- 7 days	+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days
PROCEDURES													
Informed Consent[1]	X												
Medical History	X												
Sokal & ELTS risk calculation	X												
Demographics	X												
ASC administration[2]		X+	X	X	X	X	X	X	X	X	X		
DAS administration[2]				X+	X	X	X	X	X	X	X		
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical assessment[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology bloodwork[5]	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*		X*
Biochemistry bloodwork[6]	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*		X*
Serum amylase	X	X		X			X	X	X	X	X		
Serum lipase	X	X		X			X	X	X	X	X		
Hepatitis screening	X*												
Coagulation[7]	X*												X*
HbA1C	X*												
Pregnancy test (urine)[8]	X	As clinically indicated											
Thyroid function (TSH only)	X*			X*				X*	X*	X*	X*		X*
EKG	X*	As clinically indicated											
Adverse events[9]		(Continuous)											
Concomitant medications	(Continuous)												
MOLECULAR ASSESSMENTS													

Bone Marrow Aspirate	X*	If clinically indicated									X*	X*	
Peripheral Blood RQ-PCR for BCR/ABL transcript[10]	X*							X*	X*	X*	X*		
NGS testing		X[11]										X*	

[1] Consent should be done prior to any screening assessments and according to site institutional guidelines. Site should follow their institutional guidelines for consenting window (timeframe for prior to enrollment/protocol treatment). Subject enrollment with Ozmosis Research Inc. is required. Please refer to Section 4.
[2] Refer to protocol section 6.0 for dosing information. There are no windows for treatment dosing aside from C1D1 for ASC and C2D1 for DAS.
[3] Vital signs: Pulse rate, blood pressure, temperature, and respiratory rate. Vitals will be measured prior to dosing.
[4] Clinical assessment will include assessment of height, weight, and extramedullary involvement (spleen, liver, and lymph nodes). A focused abdominal physical examination will be performed at scheduled visits to assess for clinical signs and symptoms of pancreatic toxicity, including abdominal tenderness, epigastric pain, guarding, nausea, or vomiting, to rule out pancreatitis. Physical examination will also include assessment for clinical signs of hypersensitivity, such as rash, urticaria, facial or oropharyngeal swelling, respiratory distress, hypotension, or other systemic allergic reactions. Patients will also be instructed to report any such symptoms between visits.. Height will be measured at screening only.
[5] Hematology includes complete blood count (CBC) + differential
[6] Blood chemistry includes sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, serum creatinine, urea, ALT, AST, ALP, LDH, and bilirubin
[7] Coagulation bloodwork includes INR and aPTT
[8] Only for women of reproductive potential (including women of reproductive potential whose partners are sterilized). Required at baseline, as clinically indicated thereafter.
[9] Adverse Events will be coded as per CTCAE version 5.0. The AE reporting period begins at the time the patient receives their first dose of study treatment. All AEs and SAEs must be followed until resolution or 30 days following the last dose of study treatment, whichever comes first
[10] BCR::ABL1 transcript level analysis will be performed using local PCR test in each study center's laboratory
[11] To be performed at the central lab at Toronto General Hospital. Please see Lab Manual for further instructions.
[12] Only required for combination arm ASC + DAS
[13] EOT either due to progression, treatment failure or intolerance. Note that the EOT visit does not need to be performed for patients who attend the C12D28 visit.
* To be performed per standard of care
[+] Window to administer drug is +/- 3 days