VERSION HISTORY (to be completed once finalised)

Version	**Effective Date**	**Change Type** (New, Revise, Admin)	**Summary of Revisions**
V1	17/6/20	New	N/A

Non-Interventional Study Protocol

X9001222

A retrospective chart review of UK patients with relapsed/refractory acute lymphoblastic leukaemia treated with inotuzumab ozogamicin, a real-world research study

Statistical Analysis Plan (SAP)

Version: 1.0

Author: PPD

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TABLE OF CONTENTS

LIST OF FIGURES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

To be completed for any changes made post-finalisation

2. TABLE OF ABBREVIATIONS

Abbreviation	Definition
ALL	Acute Lymphoblastic Leukaemia
CR	Complete Remission
InO	Inotuzumab Ozogamicin
MRD	Minimal Residual Disease
VOD	Veno-occlusive Disease
SOS	Sinusoidal Obstruction Syndrome
TRAE	Treatment Related Adverse Event
HSCT	Hematopoietic Stem Cell Transplant
EMA	European Medical Agency
UK	United Kingdom
NICE	National Institute for Health and Care Excellence
CUP	Compassionate Use Program
NHS	National Health Service
SAP	Statistical Analysis plan
CRi	Complete Remission with incomplete hematological recovery
OS	Overall Survival
RFS	Relapse-free Survival
NRM	Non-relapse Mortality
CAR	Chimeric Antigen Receptor
ECOG	Eastern Cooperative Oncology Group
ANC	Absolute Neutrophil Counts
ALT	Alanine Transaminase (also known as alanine aminotransferase)
AST	Aspartate Transaminase (also known as aspartate aminotransferase)
ALP	Alkaline Phosphatase
GGT	Gamma-Glutamyl Transferase
CCI	CCI
eCRF	Electronic Case Report Form
MLL	Mixed Lineage Leukaemia
IQR	Interquartile range
CI	Confidence Interval
AE	Adverse Event
NI	Non-Interventional

3. INTRODUCTION

Note: in this document any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

Inotuzumab ozogamicin (InO) is a CD22 monoclonal antibody that was shown to improve outcomes of patients with relapsed/refractory B-cell acute lymphoblastic leukaemia (ALL) or Philadelphia chromosome positive ALL. In the phase III INO-VATE ALL study, patients receiving InO versus standard chemotherapy achieved significantly higher complete remission (CR) rates and minimal residual disease (MRD)-negativity rates. Veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) was reported in INO-VATE ALL as a treatment related adverse event (TRAE), on average two weeks after end of treatment with InO, and especially in patients who had follow-up hematopoietic stem cell transplant (HSCT) therapy.

InO was approved by the European Medicines Agency (EMA) in June 2017. InO recently gained recommendation from the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) in line with the licensed indication on 9th August 2018 and is now available in routine care practice throughout the UK. Prior to NICE approval, InO was made available to UK patients through a compassionate use program (CUP) run by Pfizer Inc. between June 2016 and October 2017, and via private purchase. As part of the CUP alone, approximately 75 patients were treated across 31 National Health Service (NHS) Trusts, each Trust treating between 1 and 15 patients. Patient level data is available in medical records, enabling a retrospective chart review to be conducted.

There is a paucity of information on clinical outcomes in UK patients with relapsed/refractory B-cell ALL treated with InO outside of the context of clinical trials. The number of patients enrolled in INO-VATE ALL from the UK was limited. In this context, a retrospective chart review evaluating real world effectiveness and safety of InO for ALL when administered in routine care in the UK is of interest to clinicians and patients.

3.1. Study Design

This is a UK, multi-centre, retrospective, non-interventional cohort study based on secondary use of hospital medical records (paper-based and/or electronic, as appropriate). Three to five out of the 31 NHS Trusts that treated the largest number of patients with InO as part of the CUP will be initially selected for this study (the number of centres may be further expanded). A retrospective design has been selected as data have already been recorded into medical records and are available for data collection. The study is non-interventional as all patients received InO as part of routine clinical care, either via enrolment into the CUP or via private purchase.

3.1.1. Key Definitions

- *Index date: the date of initiation of the first cycle of InO.*

- *Baseline period: period from 6 months prior to index date. The closest observation recorded during the baseline period to the index date will be used as baseline data (when more than one observation is available).*

- *Pre-index observation period: period from the date of ALL diagnosis to the index date.*

- *Post-index observation period: period from the index date until the date of death, or date of latest visit at the time of data collection, whichever is soonest.*

- *CR/CRi rate: number of patients who achieve CR/CRi divided by the total number of patients completing treatment with InO (defined as patients with a recorded date of discontinuation of InO).*

- *MRD negativity rate: proportion of patients in whom MRD-negative status is observed, among patients in whom MRD negativity status has been assessed, at any time until the end of treatment with InO (defined as the date of recorded discontinuation of InO).*

- *OS: time from index date to death.*

- *RFS (interchangeable with EFS for the purpose of this SAP): time from index date to the earliest date of the following events: death, progressive disease (including objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status) and start of new induction therapy or posttherapy HSCT without achieving CR/CRi.*

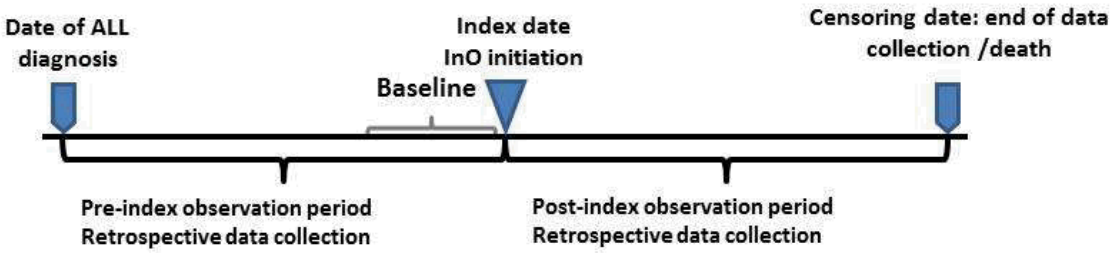
- *NRM: Time from the date of follow-up HSCT until death without disease progression or relapse. Deaths from any cause without prior progression are events. Events related to the disease such as relapse, progression are competing events, loss of follow-up are censored.*

Patients will be observed from the start of the pre-index observation period until the end of the post-index observation period. For the purpose of identifying risk factors for VOD/SOS and replicating the findings by Kantarjian et al[1] follow-up will be defined as the post-index observation period, and patients will be censored at the date of the last recorded clinic visit prior to data collection.

For the estimation of endpoints, the following definitions will be implemented. The index date will be defined as the date of initiation of the first cycle of InO. CR/CRi rate will be defined as the number of patients who achieve CR/CRi divided by the total number of patients completing treatment with InO (defined as patients with a recorded date of discontinuation of InO). The MRD negativity rate will be defined as the proportion of patients in whom MRD-negative status is observed, among patients in whom MRD negativity status has been assessed, at any time until the end of treatment with InO (defined as the date of recorded discontinuation of InO). OS will be defined as the time from index date to death,

RFS will be defined as the time from index date to the earliest date of the following events: death, progressive disease (including objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), and start of new induction therapy or post-therapy HSCT without achieving CR/CRi. NRM will be defined as the time from date of follow-up HSCT until death without disease progression or relapse. Deaths from any cause without prior progression are events. Events related to the disease such as relapse or progression are competing events. Patients who are lost to follow-up will be censored at the last known visit date. Patients who are still alive at the study cut-off date (31st December 2020) or the last visit date available will be censored (at whichever occurred first).

Figure 1. Study design and observation periods



The baseline period is 6 months prior to the index date. All other time periods shown are variable for each patient.

3.1.2. Study Population

The source population for this study is adult patients treated with InO at the selected sites and who accessed InO via NHS commissioning, via the CUP or via private purchase between June 2016 and date of data collection (December 31st 2020). The NICE recommendation is as an option for treating relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia in adults; and patients with relapsed or refractory Philadelphia chromosome positive disease should have had at least 1 tyrosine kinase inhibitor. The eligibility criteria for inclusion into the CUP is provided in Section 16 Annex 1 of the study protocol.

Patients will be eligible for inclusion in the present study if they fulfil all the following criteria:

Inclusion Criteria

- *Patients with relapsed/refractory ALL.*
- *Patients who initiated InO between 1st of June 2016 and date of data collection (to be confirmed).*

- *Patients who accessed InO treatment via NHS commissioning, via the CUP, or via private purchase.*

- *Patients aged ≥18 years old at initiation of InO treatment.*

Exclusion Criteria

- *Patients initiated on treatment with InO at a different hospital than the ones selected in this study.*

- *Patients with <3 months of follow-up since index date, unless death occurs <3 months from index date.*

Consent will not be required as all identifiable patient data (from surviving and deceased patients) will be extracted by the patient's direct medical care team. Eligible patients will be selected by chronological order and with a priority given to patients treated via NHS commissioning, where possible.

3.1.3. Data Source

Data for this study will be initially collected through retrospective data collection from three to five NHS Trust cancer services in the UK which were part of the CUP (additional centres may be added at a later stage if the target sample size is not achieved). The sample size of approximately 25 patients has been based on the number of patients expected to be available at three centres that individually treated the largest number of patients with InO. Further detail regarding sample size can be found in section 9.5 of the study protocol.

Data on patient demographic and clinical characteristics, treatment patterns, outcomes, and AEs will be collected from paper based and/or electronic hospital medical records (as applicable at each site) by members of the patient's direct care team in anonymised-coded form.

Data will be collected using anonymized-coded eCRFs designed specifically for the study. Participants will be identified in all study records by a unique participant identification number to allow data management queries to be resolved with reference to source medical records while preserving patient confidentiality.

4. STUDY OBJECTIVES

The purpose of this study is to describe the demographics and clinical characteristics, treatment pathway, and effectiveness and safety of InO in patients with relapsed/refractory B-cell ALL treated with InO in the real-world.

The objectives of the study are as follows.

Primary Objective:

- *To describe the baseline demographic, clinical (including previous treatment) and laboratory characteristics of patients with relapsed/refractory B-cell ALL at initiation of treatment with InO.*

Secondary Objectives:

- *To describe the InO treatment pathway, including InO doses, dose modifications and number of cycles of treatment; and concomitant medications.*
- *To summarise CR or CR with incomplete haematological recovery (CR/CRi) rates at completion of treatment with InO, overall and stratified according to the number of salvage therapies (0, 1, ≥2) received prior to InO initiation.*
- *To summarise MRD negativity rates in patients assessed for MRD negativity, at completion of treatment with InO, and describe the number of cycles of InO needed to attain MRD negativity.*
- *To describe overall survival (OS), and cause of death; in all patients with or without subsequent HSCT.*
- *To describe overall HSCT rate and rate in patients going directly into HSCT (eg, without another induction therapy).*
- *To describe RFS; in all patients and in patients with or without follow-up HSCT. Additionally, to describe non-relapse mortality (NRM) in patients undergoing follow-up HSCT.*
- *To describe the treatments for ALL and responses to treatment post InO, including HSCT, chemotherapy regimens and chimeric antigen receptor T-cell therapy.*
- *To describe the occurrence of safety events including documented diagnoses of VOD/SOS, grade 3/4 TRAEs (lung/cardiac/kidney) and other liver dysfunction following InO initiation; in all patients and in patients with or without follow-up HSCT. In addition, to evaluate associations between risk factors identified in the INO-VATE ALL trial (pre-HSCT AST or ALT level ≥ ULN, pre-HSCT bilirubin ≥ ULN, use of dual-alkylating agents as transplant conditioning).and risk for VOD/SOS in patients with follow-up HSCT.*

5. INTERIM ANALYSES

According to the study protocol, there are currently no interim analyses planned for this study.

6. HYPOTHESES AND DECISION RULES

6.1. Statistical Hypotheses

This is a descriptive study and there is no a priori hypothesis specified.

6.2. Statistical Decision Rules

N/A

7. ANALYSIS SETS/POPULATIONS

*The source population for this study is adult patients treated with InO at the selected sites and who accessed InO via NHS commissioning, via the CUP or via private purchase between June 2016 and February 2019. The NICE recommendation is as an option for treating relapsed or refractory CD22- positive B-cell precursor ALL in adults; and patients with relapsed or refractory Philadelphia chromosome positive disease should have had at least 1 tyrosine kinase inhibitor9 (see **Annex 1** of the protocol for NICE eligibility criteria). The eligibility criteria for inclusion in the CUP are provided in Annex 1 of the protocol.*

7.1. Full Analysis Set

The full analysis set will be comprised of medical records extracted for the purpose of the study from all eligible patients who are enrolled into the study.

7.2. Safety Analysis Set

The safety analysis set will be comprised of medical records extracted for the purpose of the study from all eligible patients who are enrolled into the study and have at least one dose of study medication.

7.3. Subgroups

Where sample size allows (n >5), the following endpoints will be analysed overall and separately for the subgroups stated below. The analyses will follow the methods described in Section 10.1. More detail on the criteria for each subgroup can be found in Section 9 where applicable.

Outcome	Supports Protocol Objective Number	Subgroups
CR, CRi and CR/CRi response rates by the end of InO treatment	Secondary Objective 2	Overall, and by number of salvage therapies in the pre-index observation period (0,1, ≥2).
Number and proportion of patients achieving MRD negativity	Secondary Objective 3	Overall, and by number of completed cycles of InO and by number of salvage therapies in the pre-index observation period (0,1, ≥2).
Number and proportion of patients surviving at 3,6 and 12 months after InO initiation	Secondary Objective 4	Overall, and separately in patients with and without follow-up HSCT and by number of salvage therapies in the pre-index observation period (0,1, ≥2).

Outcome	Supports Protocol Objective Number	Subgroups
Cause of death	Secondary Objective 4	Overall, and separately in patients with and without follow-up HSCT.
Median OS (95% CI)	Secondary Objective 4	Overall, and separately in patients with and without follow-up HSCT.
Proportion of patients who are relapse free at 3, 6 and 12 months after InO initiation	Secondary Objective 5	All patients, separately in patients with follow-up HSCT.
Median RFS (95% CI)	Secondary Objective 5	All patients, separately in patients with follow-up HSCT.
Proportion of patients initiated on each treatment	Secondary Objective 6	Per treatment (chemotherapy (blinatumomab, other). HSCT, CAR T-cell therapy).
Response to treatment	Secondary Objective 6	Overall, and per treatment (chemotherapy (blinatumomab, other). HSCT, CAR T-cell therapy).
Survival following treatment	Secondary Objective 6	Per treatment (chemotherapy (blinatumomab, other). HSCT, CAR T-cell therapy).
Number and proportion of patients experiencing VOD/SOS during the post-index observation period	Secondary Objective 7	All patients, and in the following subgroups: no HSCT prior to InO, at least 1 HSCT prior to InO, no post-InO HSCT and patients with at least 1 HSCT post-InO. Patients will be assigned to one of these 4 groups which will be analysed separately. For each group , grade of VOD/SOS and follow-up treatment (Follow-up chemotherapy after completion of chemotherapy and follow-up HSCT after HSCT) will be presented.
Treatments received for VOD/SOS	Secondary Objective 7	All patients, separately in patients with follow-up HSCT.
Survival following treatment	Secondary Objective 7	All patients, separately in patients with follow-up HSCT.
Number and proportion of patients experiencing grade 3 or 4 TRAEs	Secondary Objective 7	All patients, separately in patients with follow-up HSCT.
Treatments received for grade 3 or 4 TRAE	Secondary Objective 7	All patients, separately in patients with follow-up HSCT.
InO dose delay as a result of grade 3 or 4 TRAE	Secondary Objective 7	All patients, separately in patients with follow-up HSCT.
Number and proportion of patients experiencing other liver dysfunctions (all grades)	Secondary Objective 7	All patients, separately in patients with follow-up HSCT.
Treatments received for other liver dysfunction	Secondary Objective 7	All patients, separately in patients with follow-up HSCT.
InO dose delay as a result of other liver dysfunction	Secondary Objective 7	All patients, separately in patients with follow-up HSCT.
Peripheral blood blast counts prior to follow-up HSCT	Secondary Objective 7	All patients, separately in patients with follow-up HSCT.

Outcome	Supports Protocol Objective Number	Subgroups
Number and proportion of patients with significant risk factors for VOD/SOS	Secondary Objective 7	Where patient numbers allow, all patients, separately in patients with follow-up HSCT.

8. ENDPOINTS AND COVARIATES

The following endpoints will be estimated.

Primary objective: To describe the baseline demographic, clinical (including previous treatment) and laboratory characteristics of patients with relapsed/refractory B-cell ALL at initiation of treatment with InO.

Summary measures of:

- *Demographic characteristics:*
  - *Age at index date;*
  - *Sex.*
- *Clinical characteristics:*
  - *ECOG performance status at baseline;*
  - *Time between ALL diagnosis and index date;*
  - *Phase of disease at index date: CR, 1st relapse, 2nd relapse, 3rd relapse, 4th or greater relapse;*
  - *CD22 expression: percentage of positive cell blasts;*
  - *ALL cytogenetics; mixed lineage leukaemia (MLL)-AF4; BCRABL; low hypodiploidy/near triploidy; complex karyotype;*
  - *Number of ALL relapses prior to index date;*
  - *History of liver diseases prior to index date (before or after diagnosis), and whether they were ongoing or resolved at index date.*
- *Laboratory characteristics at baseline:*
  - *Full blood counts, including platelets and ANC;*

- *Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, albumin, gamma glutamyl transferase (GGT).*

- *ALL-related treatment prior to InO initiation:*
  - *1st line chemotherapy according to national trial or treatment guideline;*
  - *Summary of number of patients by;*
    - *Number of lines of salvage therapy: 0, 1, 2, ≥3;*
    - *Number of prior HSCT (0, 1, 2, ≥3);*
    - *Type of conditioning regimen for each HSCT (high dose myeloablative, reduced intensity, nonmyeloablative;*
    - *Treated with blinatumomab;*
    - *Number of CAR T-cell therapies: 0, 1, ≥2.*

Secondary objective* 1*: To describe the InO treatment pathway, including InO doses, dose modifications and number of cycles of treatment; and concomitant medications.

- *Total duration of treatment with InO;*
- *Number of cycles of InO per patient;*
- *Interrupted cycles of InO, including reasons (liver toxicity TRAEs, other AEs, tolerance, treatment failure, and course complete);*
- *Doses of InO prescribed;*
- *Modification of doses of InO, including reasons (liver toxicity TRAEs, other AEs, tolerance, treatment failure, and course complete);*
- *Azole antifungal therapy concomitant to InO treatment.*

Secondary objective* 2*: To summarise CR/CRi rates following initiation of InO, overall and according to the number of salvage therapies received prior to InO initiation.

Summary measures of:

- *CR, CRi and CR/CRi response rates by the end of InO treatment, overall and according to the number of salvage therapies in the pre-index observation period (0, 1, ≥2).*

- *Median time to CR/CRi (95% CI).*

Secondary objective 3: To summarise MRD negativity rates following initiation of InO and describe the number of cycles of InO needed to attain MRD negativity.

- *Number and proportion of patients achieving a MRD negative CR/CRi overall and by the number of completed cycles of InO (after 1, 2, ≥3 cycles of InO) in patients evaluated by flow-cytometry/ molecular assessment / both.*

Secondary objective 4: To describe OS, and cause of death; in all patients and in patient with or without follow-up HSCT.

- *The number and proportion of patients surviving at 3, 6 and 12 months after InO initiation;*
- *Cause of death;*
- *Median OS (95% CI).*

Secondary objective 5: To describe RFS in all patients and in patients with or without follow-up HSCT. Additionally, to describe NRM in patients undergoing follow-up HSCT.

- *The number and proportion of patients who are relapse-free at 3, 6 and 12 months after InO initiation;*
- *Median RFS (95% CI).*

In patients undergoing follow-up HSCT:

- *Median NRM (95% CI) from the date of follow-up HSCT.*

Secondary objective 6: To describe the treatments for ALL and responses to treatment post-InO, including HSCT, chemotherapy regimens and CAR T-cell therapy

For each treatment post-InO including new chemotherapy (blinatumomab, CarT, other), HSCT, CAR T cell therapy, report:

- *Number and proportion of patients initiated on treatment (for HSCT report number of HSCT);*
- *Response to treatment: CR, CRi, progressive disease, stable disease;*
- *Survival: number of patients alive / dead at completion of treatment.*

Secondary objective 7: To describe the occurrence of safety events including documented diagnosis of VOD/SOS, grade 3/4 TRAEs (lung/cardiac/kidney) and other liver dysfunction following InO initiation; in all patients and in patients with or without follow-up HSCT. In addition, to evaluate associations between risk factors identified in the INO-VATE ALL trial and risk for VOD/SOS in patients with follow-up HSCT.

Summary measures of, in all patients, and separately in patients with and without follow-up HSCT:

- *Number and proportion of patients experiencing a documented diagnosis of VOD/SOS during the post-index observation period, overall, by grade, and in the subsets of patients (1) with follow-up chemotherapy after completion of chemotherapy, and (2) with follow-up HSCT after HSCT* Separate;
- *Treatments received for documented diagnoses of VOD/SOS including defibrotide and heparin and survival following treatment (patient alive / dead, cause of death);*
- *Number and proportion of patients with InO discontinuation due to VOD/SOS;*
- *Number and proportion of patients experiencing grade 3/4 TRAEs (following InO initiation, by type;*
- *Treatments received and InO dose delay/reduction/discontinuation for grade 3/4 TRAEs (lung/cardiac/kidney);*
- *Number and proportion of patients experiencing other liver dysfunction following InO initiation);*
- *Treatments received and InO dose delay/reduction/discontinuation for other liver dysfunction;*
- *Peripheral blood blast counts of patients prior to follow-up HSCT;*
- *Number and proportion of patients with significant risk factors for VOD/SOS measured at the time of follow-up HSCT, separately in patients developing and not developing VOD/SOS.*

Secondary objective 8: To describe overall HSCT rate and rate in patients going directly into HSCT (eg, without another induction therapy)

Exploratory endpoint:

- CCI [redacted]

9. HANDLING OF MISSING VALUES

Where dates are ambiguous because of missing day and/or months, standard imputation will be applied: where day is missing the 15th of the month will be assumed; where both day and month are missing the 1st July will be assumed if appropriate to the analysis being conducted. The imputed dates for pre-index records will be reviewed to confirm they are prior to the index date, and the imputed dates for post-index records will be reviewed to confirm they are after the index date. Where data other than dates are missing from the original medical record, the affected analyses will be conducted using only the results of those patients with data available and the number included in each analysis will be stated. The percentage of data missing will be reported for each study variable. Note that the multivariate model will only include those patients with non-missing values for all covariates.

10. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

10.1. Statistical Methods

The following statistical methods will be used:

10.1.1. Analysis for Quantitative Data

Quantitative data will generally be analysed using basic summary statistics of central tendency (including numbers, means and medians), number of missing and non-missing values and dispersion (including standard deviations, the interquartile range [IQR] and the range). If data are normally distributed (evaluated through inspection of histograms), 95% confidence intervals will be calculated, otherwise the IQR will be presented instead.

10.1.2. Analysis for Categorical Data

For categorical data, the number, frequency and percentage tables will be presented. The number of missing and non-missing values will be presented.

10.1.3. Analysis for Ordinal Data

For ordinal data, summary statistics of central tendency (including numbers, means and medians), the number of missing and non-missing values and dispersion (including standard deviations, IQRs and the range) will be presented along with frequency and percentage tables.

10.1.4. Analysis for Binary Endpoints

Most binary endpoints will be summarized using frequency tables with numbers, percentages and the number of missing and non-missing values.

10.1.5. Analysis for Time-to-event-data

For survival-related endpoints, Kaplan-Meier analysis will be used where appropriate. Summary tables of the number of events and censored patients at each month interval will also be included.

95% Confidence Intervals for median survival will be estimated using the method of Brookmeyer and Crowley or another appropriate method depending on the statistical programme being used to conduct the analysis. Swimmer plots will be used to show individual patient response to treatment over time (CR, PR, stable disease, progressive disease); these are plots that display a range of information with bars indicating the length of follow-up for each individual patient and symbols on the bars showing where CR and PR are reached and end.

10.2. Statistical Analyses

10.2.1. Primary Objective

To describe the baseline demographic, clinical (including previous treatment) and laboratory characteristics of patients with relapsed/refractory B-cell ALL at initiation of treatment with InO.

Age, duration from ALL diagnosis to index date, CD22 expression, full blood counts and liver function test results will be summarised as quantitative variables (see Section 10.1.1), measures of central tendency (mean and median) and dispersion (standard deviation, IQR and range) and the number of non-missing and missing values will be calculated. Age at index date will be calculated as the difference between index date and date of birth. As only month and year of birth will be collected for data privacy reasons, the day of date of birth will be inferred as the 15th of the month as per the missing data section (see Section 7). Sex, phase of disease at index date, ALL cytogenetics, history of liver disease at index date, 1st line chemotherapy according to national trial or treatment guideline and conditioning regimen for each HSCT will be summarised as categorical variables (see Section 10.1.2). ECOG performance status at index, number of ALL relapses prior to index date, number of lines of salvage therapy, number of prior HSCTs and number of CAR T-cell therapies will be summarised as ordinal variables (see Section 10.1.3). Whether the patient was treated with blinatumomab will be summarised as a binary variable (see Section 10.1.4). Overall HSCT rate will be calculated as the number of patients with.

10.2.2. Secondary Objective 1

To describe the InO treatment pathway, including InO doses, dose modifications and number of cycles of treatment; and concomitant medications.

Total duration of treatment with InO will be summarised as a quantitative variable (see Section 10.1.1); measures of central tendency (mean and median) and dispersion (standard deviation, interquartile range [IQR] and range) and the number of non-missing and missing values will be calculated. The number of cycles of InO per patient, the number of interrupted cycles of InO, doses of InO prescribed and the modification of doses of InO will be summarised as ordinal variables (see Section 10.1.3). Reasons for interruption and modification of InO cycles and azole antifungal therapies concomitant to InO treatment will be summarised as categorical variables (see Section 10.1.2). The proportion of patients who temporarily or permanently stopped InO treatment due to an AE will be presented as proportions and percentages.

10.2.3. Secondary Objective 2

To summarise CR/CRi rates following initiation of InO, overall and according to the number of salvage therapies received prior to InO initiation.

The CR/CRi rate will be estimated as the proportion of patients who achieve CR/CRi divided by the total number of patients completing treatment with InO (defined as patients with a recorded date of discontinuation of InO). Patients who have not completed treatment with InO or do not have a recorded discontinuation date will not be included. Patient response to treatment will be presented as a binary variable (see Section 10.1.4). Response rates will be presented overall and by number of salvage therapies in the pre-index observation period (0,1, ≥2). Kaplan-Meier analysis will be utilised to analyse time to CR/CRi and the median time to CR/CRi, as well as 95% CI, will be calculated using the Kaplan-Meier method and presented as per Section 10.1.5.

10.2.4. Secondary Objective 3

To summarise MRD negativity rates following initiation of InO and describe the number of cycles of InO needed to attain MRD negativity.

The proportion of patients achieving MRD negativity overall and by the number of completed cycles will be presented as a binary variable (see Section 10.1.4), with the denominator being the total number of patients for whom MRD negativity has been assessed and who have achieved CR/CRi, at any time until the end of treatment with InO (defined as the date of recorded discontinuation of InO. The method of MRD negativity evaluation will be presented as a categorical variable (see Section 10.1.2). This definition of the MRD denominator supersedes the earlier definition detailed in the protocol and earlier in this SAP.

10.2.5. Secondary Objective 4

To describe OS, and cause of death; in all patients and in patient with or without follow-up HSCT.

The number and proportion of patients surviving at 3, 6 and 12 months after InO initiation will be presented as a categorical variable (see Section 10.1.2). The median OS and 95% CI will also be presented as Kaplan-Meier plots (see Section 10.1.5). Cause of death will be presented as a categorical variable (see Section 10.1.2). A summary table of the number of events and censored patients at each month interval will also be included. OS = death or date patient was last known to be alive – index date. OS will be presented in days or years as appropriate. OS in years will be calculated as the OS in days divided by 365.25. If any components required for the calculation are missing or incomplete for a patient, then that patient will be excluded from the analysis.

10.2.6. Secondary Objective 5

To describe RFS in all patients and in patients with or without follow-up HSCT. Additionally, to describe NRM in patients undergoing follow-up HSCT.

The number and proportion of patients who are relapse-free at 3,6 and 12 months after InO initiation will be presented as a categorical endpoint (Section 10.1.2). The median RFS with 95% CI will also be presented as a binary variable, using Kaplan-Meier plots (see Section 10.1.5). In patients undergoing a follow-up HSCT, the NRM from the date of follow-up HSCT will be presented as a Kaplan-Meier plot and the median NRM (95% CI) will be calculated. The analysis for this endpoint will be conducted in all patients and separately in patients with and without follow-up HSCT. Summary tables of the number of events and censored patients at each month interval will also be included. RFS = time of event (death, progressive disease (objective progression, relapse from CR/Cri, treatment discontinuation due to deterioration of health status), start of new induction therapy or post-therapy HSCT without achieving CR/Cri, whichever is earliest) – index date. RFS will presented in days or years as appropriate. RFS in years will be calculated as the RFS in days divided by 365.25. If any components required for the calculation are missing or incomplete for a patient, then that patient will be excluded from the analysis. NRM = Date of earliest event (see key definitions section for what is to be considered an event for this analysis)– date of earliest follow-up HSCT. NRM will presented in days or years as appropriate. NRM in years will be calculated as the NRM in days divided by 365.25. If any components required for the calculation are missing or incomplete for a patient, then that patient will be excluded from the analysis.

10.2.7. Secondary Objective 6

To describe the treatments for ALL and responses to treatment post-InO, including HSCT, chemotherapy regimens and CAR T-cell therapy.

The number and proportion of patients initiated on each treatment post-index will be tabulated and presented in the form of frequencies and percentages (Section 10.1.2). Best response while on treatment for each patient and survival at completion of treatment will be tabulated as frequencies and percentages.

10.2.8. Secondary Objective 7

To describe the occurrence of safety events including documented diagnosis of VOD/SOS, grade 3/4 TRAEs (lung/cardiac/kidney) and other liver dysfunction following InO initiation; in all patients and in patients with or without follow-up HSCT. In addition, to evaluate associations between risk factors identified in the INO-VATE ALL trial and risk for VOD/SOS in patients with follow-up HSCT.

The number of patients experiencing a documented diagnosis of VOD/SOS post-index, patients with an InO dose delay/reduction/discontinuation due to VOS/SOS, the number of patients experiencing a grade 3 or 4 TRAE (lung/cardiac/kidney) by type, treatments received for grade 3 or 4 TRAEs, dose delay/reduction/discontinuations for grade 3/4 TRAEs, the number of patients experiencing other liver dysfunctions and the associated treatments received and delay/reduction/discontinuations resulting will be presented as categoric variables (see Section 10.1.2). If sample size allows, this variable will be presented overall, and separately by grade, whether patient had follow-up chemotherapy after completion of chemotherapy or not and with follow up HSCT after HSCT or not. Treatments

for VOD/SOS will be presented as a categoric variable as per Section 10.1.2. Survival after treatment will be presented as a binary variable (see Section 10.1.4). Peripheral blood counts prior to follow-up HSCT will be presented as quantitative data (see Section 10.1.1). The number and proportion of patients with significant risk factors for VOD/SOS measured at the time of follow-up HSCT, separately in patients developing and not developing VOD/SOS will be presented as categorical variables. The methodology for the evaluation of associations between risk factors will depend on whether there is any censorship of the data, if there is censoring a cox regression model will be used, otherwise, logistic regression and odds ratios will be used instead. The proportion of patients experiencing severe cytopenia will be presented as a binary variable.

10.2.9. Secondary Objective 8

Secondary objective 8: To describe overall HSCT rate and rate in patients going directly into HSCT (eg, without another induction therapy).

Overall HSCT rate will be calculated as the number of patients who have an HSCT after discontinuing InO divided by the total number of patients who discontinue InO for reasons other than death or being lost to follow-up while on InO. The rate in patients going directly into HSCT after InO discontinuation without another induction therapy will be calculated as the number of patients who go directly into HSCT without another induction therapy divided by the number of patient who have a follow-up HSCT post-InO discontinuation. Both of the above endpoints will be presented as binary variables as per Section 10.1.4.

10.2.10. Exploratory Endpoint

CCI [redacted]

10.2.11. Summary of Analyses

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Missing Data
Summary of Age at index	All patients	Primary objective	None	Age at index date will be calculated as the difference between index date and date of birth. Summary statistics calculated (as per Section 10.1.1).	Day of birth assumed to be the 15th of the month. If month is missing, month of birth is assumed to be July, otherwise excluded.
Distribution of sex	All patients	Primary objective	None	Frequency tables and percentages.	Excluded.
Distribution of ECOG performance status at baseline	All patients	Primary objective	None	Frequency tables and percentages. Summary statistics.	Excluded.
Time between ALL diagnosis and initiation of InO (index date)	All patients	Primary objective	None	Frequency tables and percentages. Summary statistics.	Dates will be assumed to be the 15th of the month. If month is missing, month of birth is assumed to be July, otherwise excluded.
Phase of disease at index date	All patients	Primary objective	None	Frequency tables and percentages.	Excluded.
CD22 expression: percentage of positive cell blasts	All patients	Primary objective	None	Frequency tables and percentages. Summary statistics.	Excluded.
Distribution of ALL cytogenetics	All patients	Primary objective	None	Frequency tables and percentages.	Excluded.
Number of ALL relapses prior to index date	All patients	Primary objective	None	Frequency tables and percentages. Summary statistics.	Excluded.
History of liver diseases prior to index date	All patients	Primary objective	None	Frequency tables and percentages.	Excluded.
Summaries of full blood counts at baseline	All patients	Primary objective	None	Summary statistics.	Excluded.
Summaries of liver function tests at baseline	All patients	Primary objective	None	Summary statistics.	Excluded.
1st line chemotherapy according to national trial or treatment guideline	All patients	Primary objective	None	Frequency tables and percentages.	Excluded.

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Missing Data
Summary of number of lines of salvage therapy	All patients	Primary objective	None	Frequency tables and percentages. Summary statistics.	Excluded.
Number of prior HSCTs	All patients	Primary objective	None	Frequency tables and percentages. Summary statistics.	Excluded.
Type of conditioning regimen for each HSCT	All patients	Primary objective	None	Frequency tables and percentages.	Excluded.
Proportion of patients treated with blinatumomab	All patients	Primary objective	None	Frequency tables and percentages.	Excluded.
Number of CAR T-Cell therapies	All patients	Primary objective	None	Frequency tables and percentages. Summary statistics.	Excluded.
Total duration of treatment with InO	All patients	Secondary Objective 1	None	Summary statistics.	Excluded.
Number of cycles of InO, per patient	All patients	Secondary Objective 1	None	Frequency tables and percentages. Summary statistics.	Excluded.
Interrupted cycles of InO	All patients	Secondary Objective 1	None	Frequency tables and percentages. Summary statistics.	Excluded.
Summary of reasons for interruption	All patients	Secondary Objective 1	None	Frequency tables and percentages.	Excluded.
Doses of InO prescribed	All patients	Secondary Objective 1	None	Frequency tables and percentages. Summary statistics.	Excluded.
Modification of doses of InO	All patients	Secondary Objective 1	None	Frequency tables and percentages. Summary statistics.	Excluded.
Summary of reasons for InO modifications	All patients	Secondary Objective 1	None	Frequency tables and percentages.	Excluded.
Proportion of patients treated with Azole antifungal therapy concomitant to InO treatment	All patients	Secondary Objective 1	None	Frequency tables and percentages.	Excluded.
CR, CRi and CR/CRi response rates by the end of InO treatment	All patients	Secondary objective 2	Overall, and by number of salvage therapies in the pre-index	The CR/CRi rate will be estimated as the number and proportion of patients who achieve CR/CRi divided by the total number	Standard imputation for dates (see Section 7). Otherwise excluded.

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Missing Data
			observation period (0,1, ≥2)	of patients completing treatment with InO (defined as patients with a recorded date of discontinuation of InO). Patients who have not completed treatment with InO will not be included in CR/CRi rate. Kaplan-Meier analysis, time to best response (CR/CRi and CR/CRi) from the start of InO treatment to the end of InO treatment. The median with 95% CI will be calculated.	
Number and proportion of patients achieving MRD negativity	All patients	Secondary Objective 3	Overall, and by number of completed cycles of InO	Frequency tables and percentages. Summary statistics.	Excluded.
Distribution of methods used to assess MRD negativity	All patients	Secondary Objective 3	None	Frequency tables and percentages.	Excluded.
Number and proportion of patients surviving at 3,6 and 12 months after InO initiation	All patients	Secondary Objective 4	Overall, and separately in patients with and without follow-up HSCT	Frequency tables and percentages.	Excluded.
Cause of death	All patients	Secondary Objective 4	Overall, and separately in patients with and without follow-up HSCT	Frequency tables and percentages.	Excluded.
Median OS (95% confidence interval)	All patients	Secondary Objective 4	Overall, and separately in patients with and without follow-up HSCT	Kaplan-Meier analysis, median OS measured as being from the date of InO initiation to the date of death. Patients alive at end of follow-up will be censored at date of last visit.	Standard imputation for dates (see Section 7). Otherwise excluded.
Proportion of patients who are relapse free at 3, 6 and 12 months after InO initiation	All patients	Secondary Objective 5	All patients, separately in patients with follow-up HSCT	Frequency tables and percentages.	Excluded.
Median RFS (95% CI)	All patients	Secondary Objective 5	All patients, separately in patients with	Kaplan-Meier analysis, from InO initiation to date of first relapse or date of	Standard imputation for dates (see Section 7).

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Missing Data
			follow-up HSCT	last visit before data collection.	Otherwise excluded.
Median NRM (95% CI)	Patients undergoing follow-up HSCT	Secondary Objective 5	None	Kaplan-Meier analysis, from date of follow-up HSCT to date of death or the date of last visit before date of data collection. 95% CI will also be presented.	Standard imputation for dates (see Section 7). Otherwise excluded.
Proportion of patients initiated on each treatment	All patients	Secondary objective 6	Per treatment (chemotherapy (blinatumomab, other). HSCT, CAR T-cell therapy)	Frequency tables and percentages.	Excluded.
Response to treatment	All patients	Secondary objective 6	Per treatment (chemotherapy (blinatumomab, other). HSCT, CAR T-cell therapy)	Frequency tables and percentages.	Excluded.
Survival following treatment	All patients	Secondary objective 6	Per treatment (chemotherapy (blinatumomab, other). HSCT, CAR T-cell therapy)	Frequency tables and percentages.	Excluded.
Number and proportion of patients experiencing VOD/SOS during the post-index observation period	All patients	Secondary objective 7	All patients, separately in patients with follow-up HSCT, by grade and follow-up treatment (Follow-up chemotherapy after completion of chemotherapy and follow-up HSCT after HSCT)	Frequency tables and percentages.	Excluded.
Treatments received for VOD/SOS	All patients	Secondary Objective 7	All patients, separately in patients with follow-up HSCT	Frequency tables and percentages.	Excluded.
Survival following treatment	All patients	Secondary Objective 7	All patients, separately in patients with follow-up HSCT	Frequency tables and percentages.	Excluded.
Number and proportion of patients experiencing grade 3 or 4 TRAEs	All patients	Secondary Objective 7	All patients, separately in patients with follow-up HSCT	Frequency tables and percentages.	Excluded.

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Missing Data
Treatments received for grade 3 or 4 TRAE	All patients	Secondary Objective 7	All patients, separately in patients with follow-up HSCT	Frequency tables and percentages.	Excluded.
InO dose delay as a result of grade 3 or 4 TRAE	All patients	Secondary Objective 7	All patients, separately in patients with follow-up HSCT	Frequency tables and percentages.	Excluded.
Number and proportion of patients experiencing other liver dysfunctions	All patients	Secondary Objective 7	All patients, separately in patients with follow-up HSCT	Frequency tables and percentages.	Excluded.
Treatments received for other liver dysfunction	All patients	Secondary Objective 7	All patients, separately in patients with follow-up HSCT	Frequency tables and percentages.	Excluded.
InO dose delay as a result of other liver dysfunction	All patients	Secondary Objective 7	All patients, separately in patients with follow-up HSCT	Frequency tables and percentages.	Excluded.
Peripheral blood blast counts prior to follow-up HSCT	All patients	Secondary Objective 7	All patients, separately in patients with follow-up HSCT	Summary statistics.	Excluded.
Number and proportion of patients with significant risk factors for VOD/SOS	All patients	Secondary Objective 7	All patients, separately in patients with follow-up HSCT	Frequency tables and percentages. Cox regression modelling investigating risk factor association with time to VOD/SOS. Alternatively, logistic regression and odds ratios will be used depending on whether the data is censored.	Excluded.
Overall HSCT rate	Patients who discontinue InO for reasons other than death or lost to follow-up while on InO treatment	Secondary objective 8	None	Frequency tables and percentages.	Excluded.
Rate of patients going directly into HSCT	Patients with follow-up HSCT	Secondary objective 8	None	Frequency tables and percentages.	Excluded.

11. REFERENCES

1. Kantarjian HM, DeAngelo DJ, Advani AS, et al. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. Lancet Haematol 2017; 4: e387–e398.