NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	INO-TRANSIT: –**INO**tuzumab **T**reatment **R**etrospective **A**nalysis for **N**avigating tran**SI**Tion to CD19 CAR-**T**. Real-world (RWD) treatment patterns and clinical outcomes in patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL) treated with inotuzumab-ozogamicin (InO) as bridge to chimeric antigen receptor T-cell (CAR-T) therapy in Spain, the United Kingdom (UK) and the United States (US).
Protocol number	B1931044
Protocol version identifier	2.0
Date	09 May 2025
EU Post Authorization Study (PAS) register number	EUPAS1000000118
Active substance	Inotuzumab ozogamicin (InO)
Medicinal product	Inotuzumab ozogamicin [Besponsa®]
Research question and objectives	What are the demographics, clinical characteristics, treatment patterns and outcomes of R/R ALL patients treated with InO as a bridging therapy to CD19-directed CAR-T therapy in the RWD? Specifically, the following study objectives will be addressed: **Primary objective** • To describe the demographics and clinical characteristics of R/R ALL patients treated with InO as a bridging therapy to CAR-T **Secondary objective** • To describe relevant treatment effectiveness outcomes for the study population, including response to treatment, time-to-next salvage treatment and survival • To describe InO treatment patterns in the study population, including the use of InO in combination or monotherapy, timing of treatment and dosage information

Country(ies) of study	Spain United Kingdom United States
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
AEMPS	Agency of Medicines and Medical Devices
ALL	Acute Lymphoblastic Leukaemia
Allo-SCT	Allogeneic Stem Cell Transplant
BMI	Body Mass Index
CAR-T	Chimeric Antigen Receptor T-Cell
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central Nervous System
CR	Complete Remission
CRi	CR with Incomplete Haematological Recovery
CRF	Case Report Form
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
DALYS	Disability-Adjusted Life Years
DCTs	Data Collection Tools
DMP	Data Management Plan
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event Free Survival

Abbreviation	Definition
EMA	European Medicines Agency
EMD	Extramedullary Disease
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
FDA	US Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
GvHD	Graft-Versus-Host Disease
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Provider
HMA	Heads of Medicines
HPSCT	Hematopoietic Stem Cell Transplant
HRQoL	Health-Related Quality of Life
InO	Inotuzumab-Ozogamicin
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
KTE-X19	Brexucabtagene Autoleucel
MRD	Minimal Residual Disease
NI	Non-Interventional
NIS	Non-Interventional Study

Abbreviation	Definition
NNH	Number Needed to Harm
OS	Overall Survival
PASS	Post-Authorisation Safety Study
PBC	Precursor B-cell
QALYS	Quality-Adjusted Life Year
RWD	Real World
R/R	Relapsed or Refractory
SAP	Statistical Analysis Plan
SDs	Standard Deviations
SFTP	Secure File Transfer Protocol
TKI	Tyrosine Kinase Inhibitor
UK	United Kingdom
US	United States
VOD	Veno-Occlusive Disease
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title

INO-TRANSIT: –INOtuzumab Treatment Retrospective Analysis for Navigating tranSITion to CD19 CAR-T. Real-world treatment patterns and clinical outcomes in patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL) treated with inotuzumab-ozogamicin (InO) as bridge to chimeric antigen receptor T-cell (CAR-T) therapy in Spain, the United Kingdom (UK) and the United States (US).

Rationale and background

Due to the current paucity and lack of conclusive data demonstrating the use and outcomes of anti-CD22 antibody therapy (ie, InO) as a bridging therapy to CAR-T in ALL adult patients, particularly in the RWD setting, Pfizer would like to conduct a NI, chart review study to understand and describe the patient demographics, treatment patterns and clinical outcomes associated with InO when used as a bridging therapy prior to CD19 directed CAR-T cell treatment. This study could elucidate the clinical situations where and how InO can be used as well as potentially confirming the safety of this approach.

Research question and objectives

What are the demographics, clinical characteristics, treatment patterns and outcomes of R/R ALL patients treated with InO as a bridging therapy to CD19-directed CAR-T therapy in the RWD? This research question will be addressed through the following research objectives:

- (Primary objective) To describe the demographics and clinical characteristics of R/R ALL patients treated with InO as a bridging therapy for CAR-T
- (Secondary objective) To describe relevant treatment effectiveness outcomes for the study population, including response to treatment, time-to-next salvage treatment and survival
- (Secondary objective) To describe InO treatment patterns in the study population, including the use of InO in combination or as a monotherapy, timing of treatment and dosage information

Study design

The study will be an international site-led (approximately 13 sites) retrospective observational chart review, assessing the characteristics and clinical outcomes of R/R ALL patients who received InO as a bridging therapy to CAR-T. Sites will be based in the US, UK, and Spain. This non-interventional study (NIS) is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

Population

Data will be abstracted by site staff for eligible patients meeting the following inclusion criteria:

1. Patient has a clinical diagnosis of R/R (precursor B-cell (PBC)) ALL
2. Patient is aged 18 years or older at start of InO therapy
3. Patient received InO treatment as a bridge to CD19-directed CAR-T cell therapy (is defined as either patient received InO immediately prior to apheresis, and/or patient received InO after apheresis and before CAR-T cell infusion. In either case, InO was used with the aim of preventing uncontrolled disease progression and facilitating successful progression to CAR-T cell therapy. Such patients are eligible to be included even if CAR-T was not ultimately administered from index date (01 June 2017)
4. Patients with data points available for a minimum of 3 months data from the first dose of InO are eligible for inclusion within the study. Permitted exceptions to the minimum 3-month follow-up requirement include
    a. Patients who die within the 3 months
    b. Patients who proceed to a CD19 CAR-T clinical trial within the 3 months

Variables

The following variables will be captured within the electronic case report form (eCRF):

Screener: R/R B-cell ALL diagnosis, InO initiation (01 June 2017 onwards) as bridge to CAR-T, age at 1st dose of InO, patient currently (alive/deceased), 3 months follow-up data from 1st dose InO to last assessment, CAR-T completion status.

Patient demographics: biological sex, ethnicity, body mass index (BMI), date and cause of death, patient status (actively monitored/lost to follow-up).

Clinical characteristics: salvage therapy, R/R status, duration of first remission, ALL risk group/ALL genetic alterations (at ALL diagnosis; index), lab test results (index; after InO prior to CAR-T), concomitant conditions (index), Eastern Cooperative Oncology Group (ECOG) score (index), VOD diagnosis, treatment for VOD, grade of VOD, bilirubin and platelet level/count at most severe VOD, neutropenic sepsis diagnosis, VOD risk factors (index, last InO dose, CAR-T apheresis, CAR-T infusion), at R/R ALL diagnosis – extramedullary disease (EMD) diagnosis, sites of EMD, bulky EMD, central nervous system (CNS) disease.

Patient treatments and clinical outcomes prior to CAR-T treatment: current participation in clinical trial, treatments received, date of Blinatumomab initiation, Blinatumomab reason for use, Blinatumomab

refractory status, date of InO initiation, total cumulative dose of InO, date Haematopoietic stem cell transplant (HPSCT) received, response to HPSCT, InO as bridge to HPSCT.

Use of InO as bridge to CAR-T: total number of InO cycles, InO receipt as inpatient/outpatient, date of InO initiation cycle 1, InO number and dose per cycle, InO best response (1st and last InO cycle), ECOG (last InO cycle), MRD (1st and last InO cycle), MRD assessment (1st InO cycle), MRD date (last InO cycle), MRD method (1st and last InO cycle), result of MRD analysis (1st and last InO cycle), InO prescribed as monotherapy/combination with chemo or other agent (1st and last InO cycle), dose of combination agent (1st and last InO cycle), date of final InO dose.

Patient treatments and clinical outcomes during CAR-T treatment: next step in treatment post InO as bridge, CAR-T clinical trial, start date of next treatment, next treatment ongoing/discontinued, date of discontinuation, best response to next treatment, number of leukaphereses, date of leukaphereses, leukaphereses success status, number of T-cells obtained, date of lymphodepletion, date of CAR-T cell infusion, number of CAR-T cells in infusion, at CAR-T infusion - most recent bone marrow blast count, MRD status, EMD diagnosis, sites of EMD, CNS disease, disease status, type of CAR-T prescribed, B-cell recovery, start /end date of B-cell recovery, best response to CAR-T (1, 3, 6 & 12 months), most recent bone marrow blast count post CAR-T bridging.

Patient treatments and clinical outcomes after CAR-T treatment: total number of treatment lines, treatments/procedures received, start date of 1st treatment received post CAR-T, total number of HPSCTs, date of each HPSCT, prior MRD assessment, date of MRD assessment, method of MRD, result of MRD analysis, response to HPSCT, Graft-Versus-Host Disease (GvHD) diagnosis following HPSCT, type of GvHD diagnosed.

Data sources

Data will be abstracted by site staff into an eCRF.

Study size

This study is purely descriptive and there will be no limit on the sample size in terms of patients meeting the eligibility criteria. The estimated number of patients based on the feasibility study is expected to be n = 79; however, this has scope to change.

Data analysis

The study is not intended to test hypotheses and is primarily descriptive in nature, therefore descriptive analysis will be conducted to meet the majority of the pre-specified objectives. Outcomes such as overall survival (OS) will be assessed via time to event analyses, with Kaplan-Meier (KM) curves and 95% CI estimated for KM curves outputted. This will be calculated using variables in the CRF.

Data analysis will be aligned with data extracted/collected from all data sets. Where specific variables or outcomes cannot be assessed/described subgroup analyses could be conducted for a subset of patients from certain data sources.

All analyses will be conducted using Stata 17 software, version 17 or the latest available version (StataCorp, College Station, Texas).

Milestones

Start of data collection is anticipated to commence December 2024 and end in June 2025, with the final study report anticipated to be delivered in August 2025.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
2.0	09 May 2025	Administrative	Title page	Addition of the study sponsor's address based in US headquarters	Address was incorrect location based in Canada
2.0	09 May 2025	Administrative	Title page	Co-author details updated to Neil Reynold's details	Change in Director from Tom Bailey to Neil Reynolds
2.0	09 May 2025	Administrative	Title page	Title section updated	Titles combined from title page and abstract
2.0	09 May 2025	Administrative	Title page	Countries added	Countries to be included in study specified for completion
2.0	09 May 2025	Administrative	Section 1: Table of contents	Table of contents updated	Update required due to changes in rest of document
2.0	09 May 2025	Administrative	Section 2: List of Abbreviations	List of abbreviations table updated and where appropriate body of protocol	Some abbreviations were missing, others were not mentioned in body of protocol
2.0	09 May 2025	Administrative	Section 3: Responsible parties	Tom Bailey, Paul D'Amico and Fatime Qosaj removed from responsible parties Neil Reynolds, Annie Fang and Emma Reeves added	Change in current involved parties
2.0	09 May 2025	Substantial	Section 4: Abstract	Title update Study sample size updated Milestone dates updated	Titles combined from title page and abstract Ethics Committee (EC) requested sample size be updated to reflect that stated in Section 9.5 Dates updated as requested by Pfizer team to reflect current timelines
2.0	09 May 2025	Administrative	Section 6: Milestones	Milestones planned dates updated Additional text added regarding data collection	Milestones dates updated as requested by Pfizer team to reflect current timelines Additional text added requested by EC in Spain
2.0	09 May 2025	Administrative	Section 7: Rationale and Background	Text deleted	Duplication of text thus deleted

2.0	09 May 2025	Administrative	Section 9.22: Exclusion Criteria	Wording amended	Amended for clarity
2.0	09 May 2025	Administrative	Section 9.9	Wording added regarding data limitation	Data limitation described as requested by statistician
2.0	09 May 2025	Administrative	Section 10.1	Wording amended regarding personal data	Amended for clarity
2.0	09 May 2025	Administrative	Section 10.3: IRB/EC	Deletion of text regarding AEMPS	As requested by EC in Spain advising this text is now redundant as AEMPS classification is no longer required
2.0	09 May 2025	Administrative	Section 10.4: Ethical conduct of study	Addition of wording regarding ethical conduct of study, referencing the Declaration of Helsinki and Spanish Royal Decree	As requested by EC in Spain
2.0	09 May 2025	Administrative	Section 11.1: Human review of unstructured data	Addition of wording regarding AE reporting	As requested by EC in Spain
2.0	09 May 2025	Administrative	Section 12:.Plans for disseminating and communicating study results	Addition of study end definition	Definition requested by UK EC
2.0	09 May 2025	Administrative	Annex 2: ENCEPP checklist for study protocols	Title amendment	Title from title page and abstract combined
2.0	09 May 2025	Administrative	Annex 3: Additional information	Addition of site names for sites in Spain, US and UK Addition of investigator names for sites in Spain	As requested by EC in Spain

6. MILESTONES

Milestone	Planned date
Registration in the Heads of Medicines (HMA)- European Medicines Agency (EMA) Catalogues of RWD studies	16 April 2024
Start of data collection	16 December 2024
End of data collection	16 June 2025
Final study report	31 August 2025

The data collection period is expected to be from December 2024 to June 2025 and will only include data collected in a retrospective manner. Only data available within the patients' medical record at the point of data entry will be eligible for inclusion in the eCRF; no prospective data entry is included in the study design.

7. RATIONALE AND BACKGROUND

ALL is a malignancy of B or T lymphoblasts characterised by uncontrolled proliferation of abnormal, immature lymphocytes and their progenitors which ultimately leads to the replacement of bone marrow elements and other lymphoid organs resulting in a typical ALL disease pattern characteristic. ALL is the second most common acute leukaemia in adults.[1] Patients typically present with symptoms related to anemia, thrombocytopenia, and neutropenia due to bone marrow replacement with the tumor. Symptoms can include fatigue, easy or spontaneous bruising/bleeding, and infections. B-symptoms, such as fever, night sweats, and unintentional weight loss are often present but may be mild. Hepatomegaly, splenomegaly, and lymphadenopathy can be seen in up to 50% of adults on presentation. CNS involvement is indicated in around 6-9% of patients at diagnosis and can be accompanied by cranial neuropathies or symptoms, predominantly meningeal, related to increased intracranial pressure.[2]

Despite the fact that 80% of ALL occurs in children, it represents a devastating disease when occurring in adults and the incidence rate in the US is estimated at 1.6 per 100,000 people,[3] 0.88 per 1000 people in central Europe and 2.7 in western Europe.[2,4] Outcomes for paediatric patients are better than adults, with prognosis declining with increasing age.[5] Whilst dose-intensification strategies have led to significant improvement in outcomes for paediatric patients (cure rates exceeding 85%), only 30-40% of adult ALL patients will achieve long-term remission.[1] Before targeted therapies, ALL prognosis for R/R patients remains poor with OS at 5 years being only 5-10%.[6,7]

Historically, classification of ALL has attempted to account for morphology and cytogenetic profile of the leukemic blasts, with updates to this classification made in 2016.[8,9] More recent classifications/subtyping are focused on cytogenetics, immunophenotype and genetic abnormalities.[10,11] B-cell ALL accounts for around 75% of cases in adults, while T-cell ALL accounts for the remaining cases.[12] Assessment of prognosis and risk stratification is central to the management of ALL and allows the physician to determine the most appropriate initial treatment regimen as well as when to consider allogeneic stem cell transplant (Allo-SCT).[13] Typically, white blood cell count and age at time of diagnosis have been used to stratify patients, as increasing age alludes to worse prognosis. Patients over the age of 60 have particularly poor outcomes, with only 10-15% long-term survival.[13]

Treatment of adult ALL has been adapted from paediatric protocols, with chemotherapy consisting of induction, consolidation and maintenance phases, with CNS prophylaxis given throughout.[12] Despite the fact that around 85-90% of patients achieve remission after induction, there are a subset who are refractory to initial treatment, and the majority of patients that do achieve complete remission (CR) will go on to relapse.[1] Options for salvage therapy for R/R disease include cytotoxic chemotherapy, reformulated single-agent chemotherapy (eg, Clofarabine) and novel monoclonal antibodies. Estimated remission rates for conventional cytotoxic agents are around 30%; however, responses are short lived.[14] InO is a CD22-targeted antibody that is covalently linked to N-acetyl-gamma-calicheamicin dimethylhydrazide, and has been shown to produce substantial improvement in terms of response rates and attainment of minimal residual disease (MRD)-negativity.[14] InO was approved for use in Europe and the US in 2017[15,16] following promising results from the INO-VATE trial, demonstrating improved CR, duration of remission and MRD negativity with InO vs standard-of-care chemotherapy.[17] InO can be used

as bridging therapy prior to SCT in R/R PBC ALL patients, as well as a substitution strategy to either eliminate or reduce cytotoxic chemotherapy for patients ineligible for SCTs.[18]

Recent clinical development and market authorisation of CD19-directed CAR-T cell therapies has offered a potential alternative to SCT in adult R/R ALL patients.[19] The ELIANA trial that led to the approval of tisagenlecleucel CAR-T cell therapy in R/R ALL excluded patients who had received prior CD19 targeted therapy. Furthermore, InO was not approved during this time and consequently there is limited published evidence regarding InO as a bridge to CD19 directed CAR-T cell therapy.[20] Although it is clear that having <5% blasts at CAR-T infusion is associated with better outcomes, it is evident from existing literature that there is current uncertainty regarding the role of InO as a bridging therapy for CAR-T cell treatment. Mullanfiroze *et al*. conducted a retrospective chart review study including paediatric and young adult R/R ALL patients in the UK (aged 0-25 years) who had received InO pre-CAR-T cell therapy, with results compared to a control cohort of R/R ALL patients treated with tisagenlecleucel but without preceding InO. Mullanfiroze *et al*. reported that outcomes for non-InO group (patients who received CAR-T without preceding InO) were comparable to those treated on the ELIANA study but the OS of the InO-treated group was significantly lower (13% vs 86% p = 0.004). Potential explanations include impact of InO on function of CAR-T cells in vivo, or that, despite equivalent prognostic and disease status as well as therapy lines pre infusion, the InO cohort represented patients with intrinsically more resistant disease. There was also an emphasis on chemorefractory patients meaning the population may therefore not have been well balanced. In addition, the sample size for the study was small (fourteen patients) therefore interpretation of the outcomes has to be made with great caution.[21] Another recent paediatric study reported non-inferior outcomes following CD19 targeted CAR T cell therapy, when InO is used as bridging treatment.[20] The pivotal phase 2 results of ZUMA-3, an international, multicentre, single-arm, open-label study evaluated the efficacy and safety of the autologous anti-CD19 CAR-T therapy Brexucabtagene autoleucel (KTE-X19) in adult patients with R/R B-cell ALL. The study revealed KTE-X19 showed a high rate of CR or CR with incomplete haematological recovery (CRi) in adult patients with R/R B-cell ALL. The median OS was not reached in responding patients, and the safety profile was manageable. These findings indicate that KTE-X19 has the potential to confer long-term clinical benefit to adult patients with R/R CD19 positive B-ALL. The study included patients with prior InO exposure, however sample size was small (n=12) and InO was not used as bridging therapy. Despite not having data for the use of InO as a bridge to brexu-cel in ZUMA-3, there is a growing interest in using InO in this setting.[22]

Due to the current paucity and lack of conclusive data demonstrating the use and outcomes of anti-CD22 antibody therapy ie, InO as a bridging therapy to CAR-T in ALL adult patients, particularly in the real-world setting, Pfizer would like to conduct a NI, chart review study to understand and describe the patient demographics, treatment patterns and clinical outcomes associated with InO when used as bridging therapy prior to CD19 directed CAR-T cell treatment. This study could elucidate to the clinical situations where InO can be used as well as potentially confirming the safety of this approach.

This NI study is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

What are the demographics, clinical characteristics, treatment patterns and outcomes of R/R ALL patients treated with InO as a bridging therapy to CD19-directed CAR-T therapy in the RWD? This research question will be addressed through the following research objectives:

- (Primary objective) To describe the demographics and clinical characteristics of R/R ALL patients treated with InO as a bridging therapy for CAR-T
- (Secondary objective) To describe relevant treatment effectiveness outcomes for the study population, including response to treatment, time-to-next salvage treatment and survival
- (Secondary objective) To describe InO treatment patterns in the study population, including the use of InO in combination or monotherapy, timing of treatment and dosage information

9. RESEARCH METHODS

9.1. Study Design

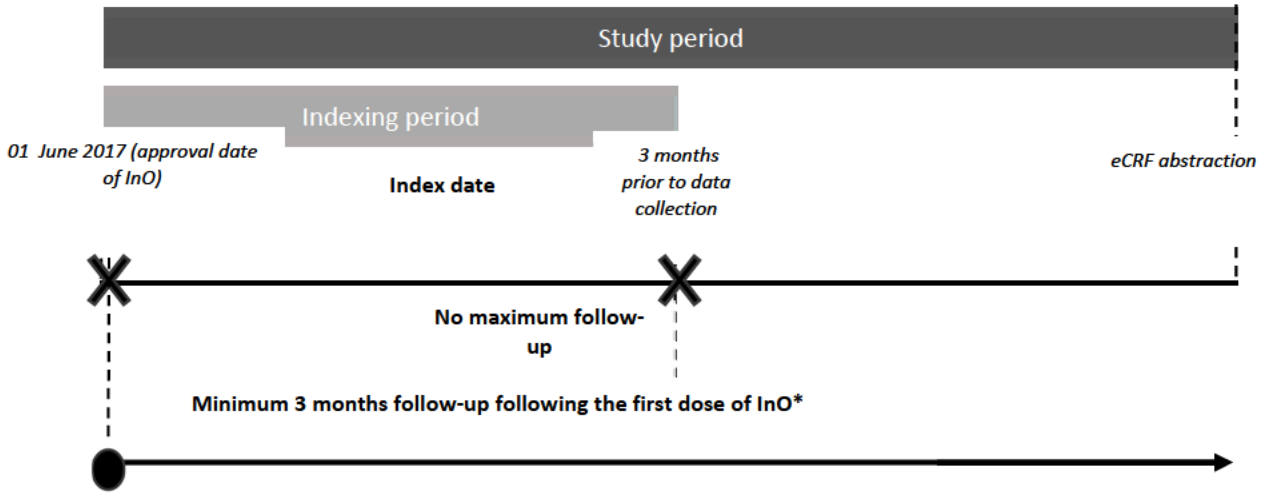
All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and HCP specialty in the countries where this NIS is being conducted.

The following study will be managed by Adelphi Real World, acting as the Clinical Research Organisation (CRO) in collaboration with Pfizer. The protocol and study methods will be reviewed by principal investigators in the UK, US and Spain to ensure scientific and clinical merit. The study will be an international site-led (approximately 13 sites) retrospective observational chart review, assessing the characteristics and clinical outcomes of R/R ALL patients who received InO as a bridging therapy to CAR-T. Sites will be based in the US, UK, and Spain. Sites will be responsible for identifying eligible patients, electronic data abstraction and data query resolution. Clinicians and site staff will abstract data from adult R/R ALL eligible patients' medical records, with index defined as those initiating InO treatment as a bridge to CAR-T from index date 01 June 2017, and enter the required datapoints within an electronic data capture (EDC) system. Baseline patient demographics and clinical and molecular characteristics will be evaluated at index. Treatment patterns and effectiveness outcomes will be described throughout the follow-up period. Patients included will be required to have a minimum follow-up of 3 months defined as patients with 3 months of data following the first dose of InO to database extraction (patients who have died within 3-months of InO administration would be considered eligible for inclusion). See Figure 1 for the study schematic.

Figure 1. Study Schematic, eCRF Design

***Permitted exceptions to the minimum 3-month follow-up requirement include:**

- Patients who die within the 3 months
- Patients who proceed to a CD19 CAR-T clinical trial within the 3 months



The study aims to assess the demographics and clinical and molecular characteristics of patients, as a primary objective. The study also aims to describe treatment effectiveness and treatment patterns as secondary objectives. See Section 8 and Section 9.3 for a breakdown of the specific endpoints and variables of interest. Details of the study period are shown in Figure 1.

9.2. Setting

R/R ALL patients aged 18 years and above initiating InO treatment as a bridge to CD19-directed CAR-T from index date 01 June 2017 (first InO approval) will be identified within the sites based in UK, US and Spain, using the inclusion and exclusion criteria specified below. The indexing period should allow for a large proportion of patients treated with InO prior to CAR-T at these sites to be gathered, following US Food and Drug Administration (FDA) and EMA approval of InO in 2017, and CAR-T approval from 2017. No formal sampling will be conducted in any country. Sites selected for chart review methodology will complete data collection for all eligible patients.

Potential sites participating in the retrospective chart review will be invited to complete a short feasibility questionnaire prior to site selection. The feasibility questionnaire will be used to confirm suitability of sites for inclusion, confirming study critical information such as InO patient caseload and data availability. Additionally, logistical information pertaining to site contracting and IRB processes will also be assessed. A number of sites across the three countries have already been assessed to provisionally confirm feasibility. Following completion of the feasibility phase of the study and the subsequent set-up activities for selected sites, eCRFs will be completed by clinicians and site staff at the sites for patients meeting the inclusion/exclusion criteria below.

9.2.1. Inclusion Criteria

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

1. Patient has a clinical diagnosis of R/R PBC ALL

2. Patient is aged 18 years or older at start of InO therapy

3. Patient received InO treatment as a bridge to CD19-directed CAR-T cell therapy (is defined as either patient received InO immediately prior to apheresis, and/or patient received InO after apheresis and before CAR-T cell infusion. In either case, InO was used with the aim of preventing uncontrolled disease progression and facilitating successful progression to CAR-T cell therapy. Such patients are eligible to be included even if CAR-T was not ultimately administered from index date (01 June 2017)

4. Patients with data points available for a minimum of 3 months data from the first dose of InO are eligible for inclusion within the study. Permitted exceptions to the minimum 3-month follow-up requirement include:

    a. Patients who die within the 3 months

    b. Patients who proceed to a CD19 CAR-T clinical trial within the 3 months

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

The CRF captures all data variables of interest therefore allowing research objectives to be addressed. Final variables will be confirmed upon finalisation of the CRF.

Screener:

Variable	Role	Data source(s)	Operational definition	Time-point
Has this patient been diagnosed with R/R B-cell leukaemia ALL?	To determine eligibility for study	eCRF	R/R (PBC) ALL diagnosis	R/R (PBC) ALL diagnosis
Patient's age (or one categorical response if aged ⩾ 90)	To determine eligibility for study	eCRF	Patients age at InO 1st dose	1st dose of InO (index)
Did the patient initiate InO treatment 01 June 2017 onwards as a bridging therapy to intended CAR-T?	To determine eligibility for study	eCRF	InO initiation as bridge to CAR-T date	1st dose of InO (index)
Is the patient currently alive?	To determine eligibility for study	eCRF	Patient's vital status	Anytime up to/including data collection

Variable	Role	Data source(s)	Operational definition	Time-point
Does the patient have at least 3 months' follow up data from the first dose of InO to the date of last assessment? *Note: Patients who die within the 3 months or proceed to a CD19 CART clinical trial are eligible for inclusion within the study*	To determine eligibility for study	eCRF	Follow up status	1st dose of InO (index) to date of last assessment
Has the patient received at least one dose of InO bridging to CAR-T therapy and then completed CAR-T therapy (if they could receive it)?	To determine eligibility for study	eCRF	InO bridging therapy status	Anytime up to/including data collection

Patient demographics:

Variable	Role	Data source(s)	Operational definition	Time-point
Patient's biological sex	Primary objective	eCRF	Patient's biological sex	N/A
Patient's race/ethnicity	Primary objective	eCRF	Patient's race/ethnicity	N/A
Patient Hispanic/Latin/Spanish origin	Primary objective	eCRF	Origin	N/A
Patient's BMI	Primary objective	eCRF	Patient's BMI at index	1st dose of InO (index)
Date of patient's death (if applicable)	Primary objective	eCRF	Time since death	Anytime up to/including data collection
Primary cause of patient's death (if applicable)	Primary objective	eCRF	Primary cause of death	Anytime up to/including data collection
Is the patient actively being monitored or have they been lost to follow up?	Primary objective	eCRF	Patient lost to follow up	Anytime up to/including data collection
Last date of activity for this patient (if lost to follow up)	Primary objective	eCRF	Time since last date of activity/ time since lost to follow up	Anytime up to/including data collection

Clinical characteristics:

Variable	Role	Data source(s)	Operational definition	Time-point
How many times has the patient received salvage therapy?	Primary objective	eCRF	Total number of salvage therapies received	Anytime up to/including data collection
On what date the patient received salvage therapy	Primary objective	eCRF	Date of each salvage therapy	Anytime up to/including data collection
Was the patient relapsed or refractory on receipt of this salvage therapy	Primary objective	eCRF	Relapse or refractory specification for each salvage therapy	Anytime up to/including data collection

Variable	Role	Data source(s)	Operational definition	Time-point
Duration of first remission following their ALL diagnosis before they relapsed? (≥12 months or <12 months)	Primary objective	eCRF	First remission duration	Since ALL diagnosis before relapse
Risk group of ALL based on cytogenic findings including: Philadelphia chromosome status, and cytogenetic, molecular and EMR positive	Primary objective	eCRF	Risk group of ALL at initial diagnosis	Initial ALL diagnosis, 1st dose of InO (index)
ALL genetic alterations	Primary objective	eCRF	ALL genetic alterations at initial diagnosis	Initial ALL diagnosis, 1st dose of InO (index
Laboratory test results	Primary objective	eCRF	Laboratory tests conducted at index	1st dose of InO (index), After the last dose of InO prior to planned CAR-T infusion
Concomitant conditions	Primary objective	eCRF	Concomitant conditions present at index	1st dose of InO (index)
ECOG performance status	Primary objective	eCRF	ECOG performance status at index	1st dose of InO (index)
Patient diagnosed with veno-occlusive disease (VOD)	Primary objective	eCRF	Presence of VOD at any time	Anytime up to/including data collection
How was the patient diagnosed with VOD?	Primary objective	eCRF	VOD diagnosis	Anytime up to/including data collection
Did the patient receive defibrotide to manage their VOD?	Primary objective	eCRF	Defibrotide received	Anytime up to/including data collection
Most severe grade of VOD patient diagnosed with	Primary objective	eCRF	VOD grade at index	Anytime up to/including data collection
Bilirubin measured at most severe VOD diagnosis	Primary objective	eCRF	Measurement of bilirubin at most severe VOD diagnosis	Anytime up to/including data collection
Bilirubin level at most severe VOD diagnosis	Primary objective	eCRF	Level of bilirubin at VOD diagnosis	Anytime up to/including data collection
Platelet count measured at most severe VOD diagnosis	Primary objective	eCRF	Platelet count at VOD diagnosis	Anytime up to/including data collection
Platelet count at most severe VOD diagnosis	Primary objective	eCRF	Platelet count result at VOD diagnosis	Anytime up to/including data collection

Variable	Role	Data source(s)	Operational definition	Time-point
Diagnosis of neutropenic sepsis	Primary objective	eCRF	Diagnosis of neutropenic sepsis	Anytime up to/including data collection
Risk factors for VOD	Primary objective	eCRF	Presence of risk factors for VOD at index	1st dose of InO (index), Last dose of InO, At CAR-T apheresis, At CAR-T infusion
EMD	Primary objective	eCRF	Presence of EMD at R/R ALL diagnosis	At R/R ALL diagnosis
Is the patient's EMD bulky (Definition: presence of a nodal mass with a maximal dimension of >10 cm, or mediastinal mass >1/3 maximum transverse diameter of the chest)	Primary objective	eCRF	Bulky EMD at R/R ALL diagnosis	At R/R ALL diagnosis
Sites of extra-medullary disease	Primary objective	eCRF	Location of EMD at R/R ALL diagnosis	At R/R ALL diagnosis
CNS disease	Primary objective	eCRF	Presence of CNS disease at R/R ALL diagnosis	At R/R ALL diagnosis
CNS disease status	Primary objective	eCRF	CNS disease status at R/R ALL diagnosis	At R/R ALL diagnosis

Patient treatments and clinical outcomes prior to CAR-T treatment:

Variable	Role	Data source (s)	Operational definition	Time-point
Is the patient currently participating in a clinical trial other than a CD19 CAR-T trial?	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Current clinical trial participation	At time of data collection

Variable	Role	Data source (s)	Operational definition	Time-point
Treatments received	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Treatments prior to InO as bridging therapy to CAR-T	Prior to InO received as a bridge to CAR-T
At what date did this patient receive Blinatumomab?	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Date received (Blinatumomab)	Prior to InO received as a bridge to CAR-T
Did the patient receive Blinatumomab for MRD conversion, R/R disease, frontline treatment or another reason?	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Reason for Blinatumomab tx	Prior to InO received as a bridge to CAR-T
Was the patient refractory to Blinatumomab?	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Was the patient refractory to Blinatumomab tx	Prior to InO received as a bridge to CAR-T
At what date did this patient receive InO? prior to it being received as a bridge to CAR-T	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Date received (InO)	Prior to InO received as a bridge to CAR-T
Total cumulative dose (mg/m^2) of InO received?	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Total cumulative dose (InO)	Prior to InO received as a bridge to CAR-T
At what date did this patient receive HPSCT?	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Initiation of therapy (HPSCT)	Prior to InO received as a bridge to CAR-T
What was the patient's response to HPSCT?	Secondary objective: To describe InO treatment patterns in the study population, including	eCRF	Response HPSCT	Prior to InO received as a bridge to CAR-T

Variable	Role	Data source (s)	Operational definition	Time-point
	chemotherapy regimen and dosage information			
Has the patient been treated with InO as a bridge to HPSCT prior to InO as a bridge to CAR-T	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	InO bridge to HPSCT	Prior to InO received as a bridge to CAR-T
Use of InO as a bridge to CAR-T				
Number of cycles of InO treatment received	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Total number of InO cycles received to date	InO received as bridge to CAR-T
Did the patient receive InO bridging to CAR-T therapy as an inpatient or outpatient?	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	InO bridging as inpatient/outpatient	InO received as bridge to CAR-T
Date of InO initiation (day 1 first dose for cycle 1)	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Date of InO initiation	InO received as bridge to CAR-T
Number of doses of InO (show per cycle)	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Number of InO doses per cycle	InO received as bridge to CAR-T
Dose of InO treatment (mg/m^2, show per dose per cycle)	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Dose of InO per dose per cycle	InO received as bridge to CAR-T
Patients' best response after InO treatment (show for first and last cycle)	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population,	eCRF	Best response after InO 1st and last cycle	InO received as bridge to CAR-T

Variable	Role	Data source (s)	Operational definition	Time-point
	including time-to-next treatment and survival			
Patients' ECOG performance status at InO treatment response evaluation (show at last cycle)	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	ECOG status after last cycle	InO received as bridge to CAR-T
Whether MRD was assessed following InO treatment (show at first and last InO cycle)	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	MRD assessment conducted per InO after 1st and last cycle	InO received as bridge to CAR-T
Date of MRD assessment following InO treatment (show for first and last InO cycle)	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Date of MRD assessment per InO after 1st and last cycle (if assessed)	InO received as bridge to CAR-T
Method used to assess MRD after InO treatment (show for first and last InO cycle)	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Method used to assess MRD after InO 1st and last cycle	InO received as bridge to CAR-T
Result of MRD analysis after InO treatment (show for first and last InO cycle)	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Result of MRD test after InO 1st and last cycle	InO received as bridge to CAR-T
Was InO prescribed in combination with chemotherapy, monotherapy and/or another combination agent eg tyrosine kinase inhibitor (TKI)? (show for first and last InO cycle)	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Prescription of chemotherapy/monotherapy/other combination agent alongside InO treatment (1st and last cycle)	InO received as bridge to CAR-T
Type of combination agent prescribed in combination with InO treatment (show for first and last InO cycle)	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Combination agent type (1st and last cycle)	InO received as bridge to CAR-T
Dose of combination agent prescribed in combination with	Secondary objective: To describe InO treatment patterns in the study	eCRF	Dose of combination agent (1st and last cycle)	InO received as bridge to CAR-T

Variable	Role	Data source (s)	Operational definition	Time-point
InO treatment (show for first and last InO cycle)	population, including chemotherapy regimen and dosage information			
Date final dose of InO received	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	InO final dose	InO received as bridge to CAR-T

Patient treatments and clinical outcomes during CAR-T treatment:

Next step after InO treatment as bridge to CAR-T	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Next step in treatment	Post InO as bridge to CAR-T
Did the patient receive CAR-T as part of a clinical trial?	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Clinical trial involvement	Post InO as bridge to CAR-T
Start date of next treatment	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Start date of next treatment	Post InO as bridge to CAR-T
Next treatment ongoing or discontinued	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Ongoing/discontinuation of next treatment	Post InO as bridge to CAR-T

Date of discontinuation of next treatment	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	End date of next treatment	Post InO as bridge to CAR-T
Patients' best response to next treatment	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Response to next treatment	Post InO as bridge to CAR-T
Time from last dose of InO to CAR-T infusion	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Time from last InO dose to CAR-T infusion	InO last dose to CAR-T infusion
Number of leukapheresis needed	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Number of leukapheresis required for CAR-T	CAR-T apheresis
Date of leukapheresis	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Date of leukapheresis for CAR-T	CAR-T apheresis
Was leukapheresis successful?	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Leukapheresis success	CAR-T apheresis
Number of T-cells obtained (CAR-T)	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	T-cell number	CAR-T apheresis
Date of commencement of lymphodepletion	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Date of lymphodepletion for CAR-T	CAR-T received post InO as bridge to CAR-T
Date of initiation of CAR T-cell infusion	Secondary objective: To describe InO treatment patterns in the study population, including	eCRF	Date of initiation of infusion for CAR-T	CAR-T infusion

	chemotherapy regimen and dosage information			
Number of CAR-T cells administered in infusion (per kg of patient)	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Number of CAR-T cells in infusion	CAR-T infusion
Most recently measured bone marrow blast count	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Most recent bone marrow blast count (CAR-T infusion)	CAR-T infusion
MRD status	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	MRD status at CAR-T infusion	CAR-T infusion
EMD	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Presence of EMD at CAR-T infusion	CAR-T infusion
Location of EMD	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Location of EMD at CAR-T infusion	CAR-T infusion
CNS disease	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Presence of CNS disease at CAR-T infusion	CAR-T infusion
Disease status (salvage 1 etc.)	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Disease status at CAR-T infusion	CAR-T infusion
Type of CAR-T prescribed	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Type of CAR-T prescribed	CAR-T received post InO as bridge to CAR-T
B-cell recovery after CAR-T infusion	Secondary objective: To describe relevant treatment	eCRF	B-cell recovery post CAR-T infusion	CAR-T received post

	effectiveness outcomes for the study population, including time-to-next treatment and survival			InO as bridge to CAR-T
Duration of B-cell recovery (start & end dates captured)	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	B-cell recovery (duration (start & end date))	CAR-T received post InO as bridge to CAR-T
Patients' response to CAR-T after 1 month	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Response to CAR-T (1 month)	CAR-T received post InO as bridge to CAR-T
Patients' response to CAR-T after 3 months	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Response to CAR-T (3 months)	CAR-T received post InO as bridge to CAR-T
Patients' response to CAR-T after 6 months	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Response to CAR-T (6 months)	CAR-T received post InO as bridge to CAR-T
Patients' response to CAR-T after 12 months	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Response to CAR-T (12 months)	CAR-T received post InO as bridge to CAR-T
Most recent bone marrow blast count	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Most recent bone marrow blast count post CAR-T bridging therapy	Post CAR-T

Patient treatments and clinical outcomes after CAR-T treatment:

Total number of treatment lines (ie, number of salvage lines) received for ALL after CAR-T bridging therapy	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information Secondary objective: To describe relevant treatment	eCRF	Treatment lines received for ALL post CAR-T	Post CAR-T

	effectiveness outcomes for the study population, including time-to-next treatment and survival			
Treatments or procedures received for ALL	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Type of treatments/procedures received for ALL post CAR-T	Post CAR-T
Time to next treatment received (start date captured)	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Time to next ALL treatment received post CAR-T	Post CAR-T
Number of HPSCTs received	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Total number of HPSCTs received	Post CAR-T
Dates HPSCTs received	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information	eCRF	Dates HPSCTs received	Post CAR-T
Was MRD assessed before this patient's HPSCT?	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	MRD assessment carried out before HPSCT	Post CAR-T
Date of the MRD assessment before this patient's HPSCT	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Date of this MRD assessment	Post CAR-T
Method(s) used to assess MRD before this patient's HPSCT	Secondary objective: To describe InO treatment patterns in the study population, including chemotherapy regimen and dosage information Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Methods used to assess MRD	Post CAR-T

Result of the MRD analysis before this patient's HPSCT	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Result of MRD analysis	Post CAR-T
Patient's response to HPSCT	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Response to SCT	Post CAR-T
Patient diagnosed with GvHD following any of their HPSCT(s)	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	Presence of GvHD following HPSCT(s)	Post CAR-T
What type of GvHD was the patient diagnosed with following any of their HPSCT(s)	Secondary objective: To describe relevant treatment effectiveness outcomes for the study population, including time-to-next treatment and survival	eCRF	GvHD classification following HPSCT(s)	Post CAR-T

9.4. Data Sources

Data will be collected/extracted from sites based in the UK, US and Spain. The study will involve the abstraction of data from patients' medical charts by healthcare professionals involved in the care of the participants into a secure eCRF. Sites will be asked to provide eCRFs for all patients which they have access to who meet the inclusion criteria. Sites will be instructed to refer to the patients' complete medical record whilst completing the eCRF and not to answer any question from memory or that is not listed within the patients' medical records.

9.5. Study Size

This study is purely descriptive and there will be no limit on the sample size in terms of patients meeting the eligibility criteria. The estimated number of patients based on the feasibility study is expected to be n = 79.

9.6. Data Management

9.6.1. Case Report Forms (CRF)/Data Collection Tools (DCTs) /Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorised representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorised third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorised staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialled, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Adelphi Real World and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

The study is not intended to test hypotheses and is primarily descriptive in nature, therefore descriptive analysis will be conducted to meet the majority of the pre-specified objectives. Frequencies and percentages will be reported for categorical variables, including the percentage of missing/unknown data, while counts, number of missing, means, medians, standard deviations (SDs), first and third quartiles, minimum and maximum values will be reported for continuous numeric variables. Where applicable, all estimates will be described with accompanying 95% confidence intervals (CI). Outcomes such as OS will be assessed via time to event analyses, with KM curves and 95% CI estimated for KM curves outputted. This will be calculated using variables in the CRF. For example, OS will be calculated from the first dose of InO to point of death. Censoring will be applied if the patient is alive at the point of data capture.

Data analysis will be aligned with data extracted/collected from all data sets. Where specific variables or outcomes cannot be assessed/described subgroup analyses could be conducted for a subset of patients from certain data sources.

All analyses will be conducted using Stata 17 software, version 17 or the latest available version (StataCorp, College Station, Texas).

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained

by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8. Quality Control

Data from the eCRF will be stored in the study database. The database will be housed and managed by ARW during the study and analysis. Any data transfers to Pfizer will be carried out via a Secure File Transfer Protocol (SFTP) to ensure any international transfers are safeguarded. ARW's data server is based within the UK. Following completion of the study, the study database will be archived and subsequently permanently deleted, in accordance with ARW's and Pfizer's Master Services Agreement.

Version control will be used during the development of all data collection materials to ensure there is an auditable record of requested updates and changes are available.

The eCRF data will be captured within a password-protected, CFR Part 11 compliant EDC platform. In addition, each individual eCRF will be reviewed by 2 members of the project team to check for logical and medical consistency. Queries will be raised throughout the data management process and will only be closed following the satisfactory correction or explanation by each site. All queries will be logged within the EDC as part of the audit trail and will also be recorded within the data management plan (DMP). Following the review and sign-off of each eCRF by 2 members of the project team, the eCRF will be locked and will not be accessible for further data entry or changes. A database lock declaration form will be completed by the project manager and the form will be kept in the study file. The locked database will be saved into a folder with restricted access. A copy of the locked database will be made available to the analyst.

9.9. Limitations of the Research Methods

- If subgroup numbers are low, comparisons will be limited. However, as this is purely a descriptive study with no statistical comparisons, the assessment of treatment patterns and effectiveness outcomes will not be affected by small sample sizes.

- InO treatment regimens and dosing schedules may differ per market, adding to the complexity of the assessment of effectiveness outcomes. Subgroup analyses could be conducted for subsets of patients receiving the same or similar treatment regimens and or dosage schedules.

- As patient data originates from multiple countries, sites and settings there may be some variability in the study results.

- The minimum follow-up period has been set to 3 months. Consequently, for a large number of patients, OS and event free survival (EFS) maybe not assessable. These patients will be censored for such analyses.

- For the chart review, selection bias may arise. Site participation is influenced by willingness to take part, and may be based on workload, levels of consulting patients during the data collection period, or familiarity with the research nature of the study. Efforts will be made to seek waivers for informed consent to prevent the requirement for consent from being a biasing factor, eg, patients who are particularly severe may be unwilling/unable to consent which may bias the living sample of patients towards those with a more positive prognosis. Efforts will therefore be made to receive a waiver for consent to mitigate this potential bias.

- Missing data from the eCRF is a potential limitation to consider in this study. Some variables that we intend to collect may not be present within a patient's medical record and so cannot be extracted into the eCRF. To address this limitation, the standardised eCRF will undergo a thorough review process prior to implementation which will help ensure that the content is appropriate for the listed research objectives and can reasonably be expected to be captured within patients' medical notes. Further, the eCRF will be designed in such a way that incomplete variables will be flagged and eCRFs will not be able to be locked until all variables have been completed. Despite these mitigations, it is expected that there will be an embargo on data from CAR-T infusion onwards for a proportion of patients (up to approximately 50%) in Spain due to an ongoing clinical trial, which will prevent data on CAR-T treatment patterns or post-CAR-T outcomes from being assessed. Nonetheless, given the paucity of data for patients receiving InO as bridging therapy to CAR-T, these patients will be included given this limitation will not impact the primary objective of the study.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorised study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorised parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorised parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the CSA and applicable privacy laws.

10.2. Patient Consent

As this study does not involve data subject to privacy laws in Spain, the UK and US according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required in these countries.

10.3. Institutional Review Board (IRB)/Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer. Ethics approval in the UK and US will be sought from a centralised ethics board/IRB, however it is likely that some sites in the US will require local IRB submissions. In Spain, per site submissions to local ECs will be conducted.

10.4. Ethical Conduct of the Study

The study will be conducted in compliance with the Declaration of Helsinki and the Spanish Royal Decree 957/2020, which regulates observational studies with medicines for human use. The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in:

- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2016; 25:2-10.

- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

- Good practices for RWD data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-International Society for Pharmacoepidemiology (ISPE) Special Task Force on RWD evidence in health care decision making

- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS)

- EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology

- The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies

- FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

- FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Human Review of Unstructured Data

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

Upon review of the medical chart in relation to this study, if sites become aware of an AE with explicit attribution to a Pfizer product (explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE with such causality documented in the medical chart), not previously reported as per the site's records, site staff are expected to fill out the AE report form that will be provided to them and forward to Pfizer Spain's pharmacovigilance team.

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

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

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

- For exposure during pregnancy in studies of pregnant women, data on the exposure to InO during pregnancy, are not reportable unless associated with serious or non-serious AEs.

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

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the

very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

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

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

- *"Your Reporting Responsibilities (YRR) with Supplemental Topics."*

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

Re-training must be completed on an annual basis using the most current YRR with Supplemental Topics training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

11.2. Structured Data Analysis

Not applicable.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The end of the study will be defined as the point in which the target sample has been achieved, data has been analyzed and a final report to discuss the findings has been produced.

Findings generated from the analyses of the study data are intended to be developed into one or more publication(s).

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

13. REFERENCES

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14. LIST OF TABLES

Not Applicable.

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes," the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a NI PASS to a regulatory authority (see the Guidance on the format and content of the protocol of NI PASS studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: INO-TRANSIT: –**INO**tuzumab **T**reatment **R**etrospective **A**nalysis for **N**avigating tran**SI**Tion to CD19 CAR-**T**. Real-world treatment patterns and clinical outcomes in patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL) treated with inotuzumab-ozogamicin (InO) bridge to chimeric antigen receptor T-cell (CAR-T) therapy in Spain, the UK and the US.

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				

Section 1: Milestones	Yes	No	N/A	Section Number
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

The dates for data collection and the final report are an estimate. These dates are dependent on contracting timelines with sites.

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is a descriptive study whereby no hypotheses are to be tested.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1/11.1
3.3 Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	7
3.4 Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of AEs /adverse reactions? (eg, AEs that will not be collected in case of primary data collection)	☒	☐	☐	11

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2
	4.2.2 Age and sex	☒	☐	☐	9.2
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

.

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorized on according to time windows?	☒	☐	☐	9.2
5.4	Is intensity of exposure addressed? (eg, dose, duration)	☒	☐	☐	9.3
5.5	Is exposure categorized on based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

This is a secondary data including ALL patients treated with InO, which is defined as the exposure. As this is a retrospective study, patients will have already received the drug and included based on this previous exposure. Patients must have received the drug during the index period (see **Section 9.2**).

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, health-related quality of life (HRQoL), quality-adjusted life year (QALYs), disability-adjusted life years (DALYS), health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

This is a purely descriptive study and outcomes assessed in this study will not be provided to HTA.

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (eg, confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

This is a purely descriptive study with no hypothesis testing, so confounding has not been addressed by design

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.9

Comments:

Potential subgroup analyses are mentioned for subsets of patients receiving the same or similar treatment regimens and or dosage schedules.

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3/9.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3/9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3/9.4

Section 9: Data sources		Yes	No	N/A	Section Number
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
	9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
	9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
	9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
	9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4	Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

Exposure, outcomes, covariates, and other characteristics are described in **Section 9.3** of the protocol. This section captures the variables which will be captured/defined through the data provided by the sites submitted via the CRF and secondary data sources. The protocol itself does not indicate the exact variables which will be provided by the data sources themselves. These will be described in detail within the study SAP.

The coding system for any exposures, outcomes or covariates is not applicable to the secondary data source or the sites where a chart review will be used for data collection. There is no linkage that will be utilised.

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7
10.4	Are stratified analyses included?	☐	☒	☐	
10.5	Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.3, 9.7 and 9.9
10.8	Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6 and 9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Quality assurance methods are captured under the quality control section of the protocol (Section 9.8)

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9

Comments:

As this study is purely descriptive and does not involve any hypothesis testing, confounding has not been addressed by design.

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of EC/ IRB been described?	☒	☐	☐	10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.5

Comments:

The ethical review procedure has not been carried out at this time.

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☐	☒	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

The study data is not currently intended to be submitted to regulatory authorities.

Name of the main author of the protocol: _____

_____

Date: dd/Month/year

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

The following sites and investigators in Spain will participate in the study:

PRINCIPAL INVESTIGATOR	SITE DETAILS
Redacted	*Hospital Clínic de Barcelona* Redacted
Redacted	Hospital General Universitario Gregorio Marañón Redacted
Redacted	Hospital Universitari Vall d'Hebron Redacted
Redacted	Hospital Universitario Virgen del Rocío Redacted
Re da	Hospital Clínico Universitario de Salamanca Redacted

The following sites from the UK and US are participating in the study:

COUNTRY	SITE
UK	The Christie NHS Foundation Trust
	Royal Marsden

	Birmingham
	Southampton
US	Seattle Cancer Care Alliance, Washington
	Medical College of Wisconsin
	Colorado

Document Approval Record

Document Name:	B1931044_NON-INTERVENTONAL STUDY PROTOCOL _V2_09May 2025
Document Title:	B1931044_NON-INTERVENTONAL STUDY PROTOCOL _V2_09May 2025

Signed By:	Date(GMT)	Signing Capacity
Redacted	30-May-2025 11:07:36	Manager Approval
Redacted	09-Jun-2025 19:48:03	Final Approval