RODEX UK Protocol Addendum

VERSION NUMBER: 2.0

DATE: 17/08/2023

RODEX: A multicentre, randomized, open-label study of romiplostim plus dexamethasone vs dexamethasone in patients with newly diagnosed primary immune thrombocytopenia

This is a European Union (EU) led study. The Sponsor has delegated certain responsibilities to the UK National Coordinator/legal representative, the UK Chief Investigator, UK Principal Investigators, UK host sites, UK coordinating Clinical Trials Unit, and other stakeholder organisations as appropriate.

The main trial protocol has been developed by the Sponsor, approved by relevant regulatory organisations in the lead country (Spain), and translated by the Sponsor into English for the purpose of clinical trial regulatory approval and delivery in the UK.

This UK Protocol Addendum has been developed by the UK National Coordinator to provide additional information to support regulatory approval and delivery of this trial at participating hospital sites in the UK only.

Sponsor	Andalusian Public Foundation for Health Research Management of Seville (FISEVI), Spain duly represented by its Managing Director José Cañon Campos, and Dr. MARIA EVA MINGOT CASTELLANO, in her capacity as Lead Investigator, member of the Clinical Management Unit of Haematology at University Hospital Virgen del Rocío (HUVR)
UK National Coordinator/Legal Representative of the Sponsor :	Cardiff University, A Registered Charitable Institution with Registered Charity Number 1136855 and whose Administrative Offices are at 30-36 Newport Road Cardiff, CF24 ODE, Wales, UK
UK CRC Registered Clinical Trials Unit (CTU) with responsibility for day to day study management in the UK:	Centre for Trials Research (CTR), Cardiff University
CTU Study Portfolio Ref:	1227
Funder:	Andalusian Public Foundation for Health Research Management of Seville (FISEVI), Spain via AMGEN's Investigator Sponsored Studies (ISS) program. IMP supply and distribution provided for free by Amgen via Alcura Health.
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IRAS number:	1007244
EudraCT ref:	2021-00690-22
ISRCTN ref:	TBC
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

UK National Coordinator/Legal Representative of Sponsor:		
Name	**Signature**	**Date**
Dr Joanna Smith, Trial Manager	Electronic by email	29.08.2023
CTR Director:		
Name	**Signature**	**Date**
Dr David Gillespie, Director I3 Trials	Electronic by email	30.08.2023
UK Chief Investigator:		
Name	**Signature**	**Date**
Dr Charlotte Bradbury	Electronic by email	30.08.2023

General Information This UK Protocol Addendum describes the RODEX clinical trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to the CTR.

UK Study Contact Details

UK Trial Email for correspondence:		RODEX@cardiff.ac.uk
UK National Coordinator Research Governance	Mrs Helen Falconer, Research Governance Officer	FalconerHE@cardiff.ac.uk resgov@cardiff.ac.uk
UK Lead/National Coordinating Chief Investigator	Dr Charlotte Bradbury, Consultant Haematologist/Senior Lecturer	Charlotte.Bradbury@uhbw.nhs.uk c.bradbury@bristol.ac.uk
CTR Study Lead	Mr Ian Thomas, Senior Trial Manager/Research Fellow	ThomasIF@cardiff.ac.uk
CTR Trial Manager:	Dr Joanna Smith, Trial Manager/Research Associate	sealjd@cardiff.ac.uk
CTR Data Manager:	Mrs Nuria Marquez Almuina, Data Manager, Research Assistant	MarquezalmuinaN@cardiff.ac.uk
CTR Study Administration:	TBC	RODEX@cardiff.ac.uk
CTR Research Governance	c/o Helen Falconer	resgov@cardiff.ac.uk

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Glossary of abbreviations

CA	Competent Authority
ICF	Informed Consent Form
CI	Chief Investigator
CTA	Clinical Trials Authorisation
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
DEX	Dexamethasone
DSUR	Development Safety Update Report
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GP	General Practitioner
IC	Informed consent
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicine and Healthcare products Regulatory Agency
mNCA	Model Agreement for Non-Commercial Research
NHS	National Health Service
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
R&D	Research and Development
REC	Research Ethics Committee
RGF	Research Governance Framework for Health and Social Care
ROM	Romiplostim
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary Product Characteristics
SOP	Standard Operating Procedure
SSA	Site Specific Assessment

SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
N/A	1.0	TBC	None – first version
N/A	2.0	TBC	Second version - added Section 2.5 Travel Expenses in response to REC review conducted 01/08/2023. Amended version number and date on front page and footers. Amended electronic authorisation dates on authorisation page. Amended Table of contents to capture changes in page numbering.

2 Synopsis

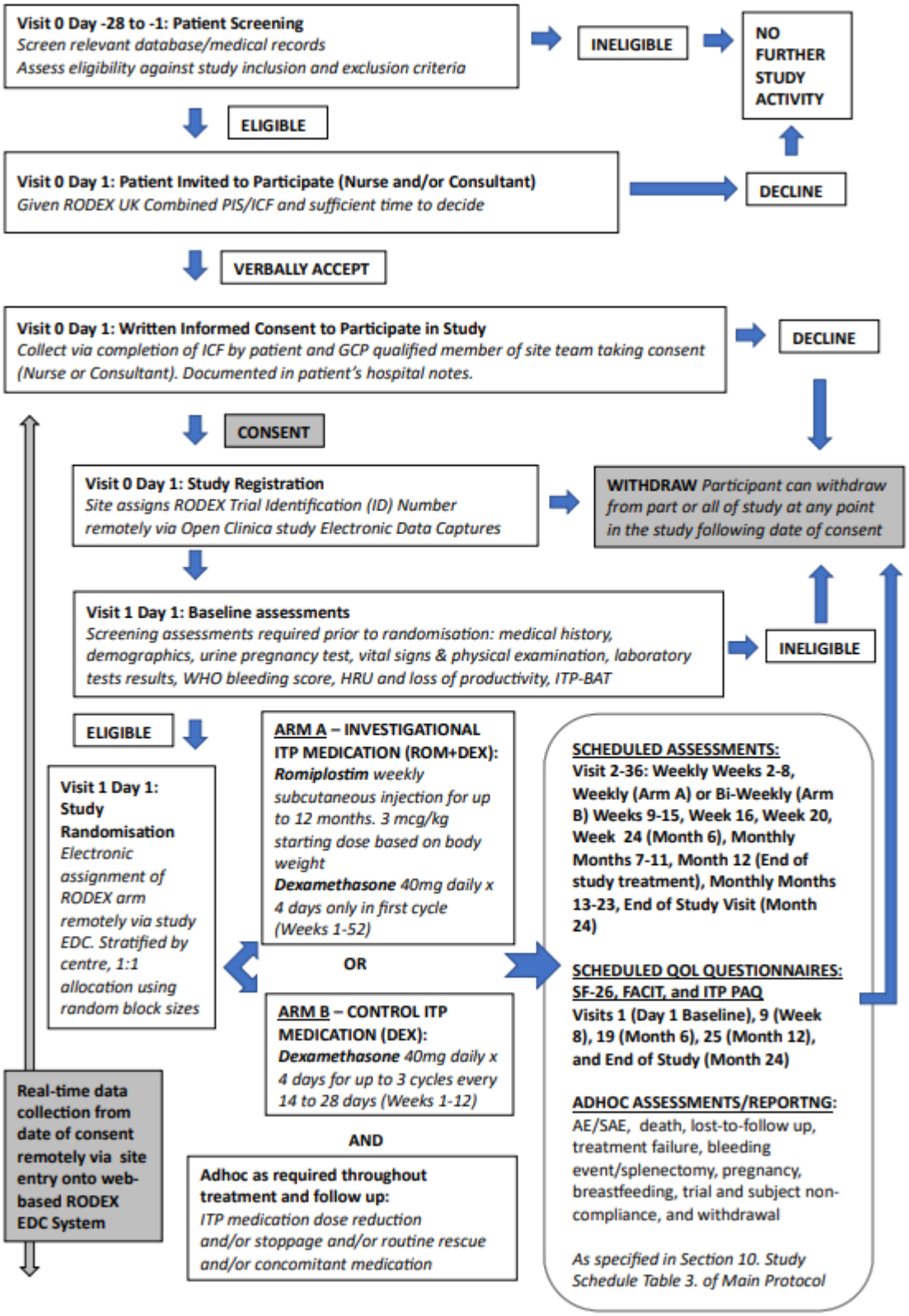
Short title	RODEX: A multicentre, randomized, open-label study of romiplostim plus dexamethasone vs dexamethasone in patients with newly diagnosed primary immune thrombocytopenia
Acronym	RODEX
Clinical phase	Phase III
IRAS number	1007244
EudraCT ref	2021-00690-22
ISRCTN ref	TBC
IRAS number	1007244
Funder	Andalusian Public Foundation for Health Research Management of Seville (FISEVI), Spain. IMP and distribution provided for free by the drug manufacturer, Amgen.
CTR Study Number	1227
Trial design	Open label, randomised, Phase 3 study to compare romiplostim plus dexamethasone vs dexamethasone alone in terms of sustained response off any ITP treatment in adult subjects with newly diagnosed ITP.
Trial participants	Adult patients with newly diagnosed ITP and a clinical indication for first line treatment
Planned sample size	Total: 126; UK (England, Wales and Scotland): 26+
Planned number of sites	UK: 10-15
Duration:	Total: 36 months Treatment: Up to 2 years Follow-up: Up to 1 year from date of last dose of IMP First patient inclusion: Last quarter 2022 Last patient inclusion: First quarter 2024 Subject participation duration: 24 months
Inclusion criteria	1) ≥18 years old at time of informed consnet 2) New diagnosis of primary ITP 3) Platelet count $<30x10^9$/L or ITP with platelet count $<50x10^9$/L and concomitant bleeding symptoms 4) Serum creatine concentration ≤1.5 mg/dL
Exclusion criteria	1) WHO performance status >2 2) Previous therapy with rituximab (within 3 months previous of study enrollment), corticosteroids or therapy with other immunomodulating agents within 1 month before enrolment; prior use of hematopoietic analogs or fostamatinib for any other reason than ITP three months before enrolment . 3) Previous use of romiplostim, PEG-recombinant human (rHu) megakaryocyte growth and development factor, eltrombopag, recombinant human antithrombopoietin (rHuTPO), or any platelet-producing agent for three months prior to enrolment. 4) Alkylating agents within 8 weeks before the screening visit or anticipated use during the time of the proposed study.

	5) Splenectomy within 3 months of the screening visit or planned splenectomy during study period. 6) Abnormal renal function (serum creatinine > 1.5 mg/dL). 7) Active hepatic disease evidenced by alanine aminotransferase [ALT] or aspartate aminotransferase [AST] levels >5 times the upper limit of normal (it will only be necessary to determine one of the two transaminases). 8) Severe chronic liver disease as evidenced by, but not limited to, any of the following: International Normalized Ratio (INR) > 1.4, hypoalbuminemia, portal vein hypertension including presence of otherwise unexplained splenomegaly and history of esophageal varices. 9) Patients with known IgM seropositive tests for cytomegalovirus and/or Epstein-Barr virus in the previous month. 10) Patients with an active viral infection at screening for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or detectable virus charge of HIV. 11) Intolerance to dexamethasone. 12) History of a bone marrow stem cell disorder. 13) Active or prior malignancy except adequately treated (i.e., complete surgical excision with negative margins) basal cell carcinoma. 14) History of Helicobacter pylori by urea breath test or stool antigen test within 6 months of enrollment, if available. 15) History of myelodysplastic syndrome, systemic lupus erythematosus, or autoimmune cytopenia. 16) History of antiphospholipid antibody syndrome. 17) History of disseminated intravascular coagulation, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura. 18) History of deep or superficial venous thromboembolism in the last 12 months or stroke, acute ischaemic heart disease or acute peripheral vascular disease in the last 6 months. 19) Hypersensitivity to any recombinant Escherichia coli-derived product (e.g., Infergen, Neupogen, Somatropin, and Actimmune) or known sensitivity to any of the products to be administered during dosing. 20) Currently enrolled in another investigational device or drug study or < 30 days since ending another investigational device or drug studies, or receiving other investigational agents. 21) Will have any other investigational procedures performed while enrolled in this clinical study. 22) Pregnant or breastfeeding, or planning to become pregnant or breastfeed during treatment or within 1 month after the end of treatment. 23) Female subject of childbearing potential is not willing to use, in combination with her partner, an acceptable method of effective contraception during treatment and for 1 month after the end of treatment (see annex 5 for additional contraception information). Females of childbearing potential should only be included after a negative pregnancy test. 24) Will not be available for protocol-required study visits, to the best of the subject's and investigator's knowledge.

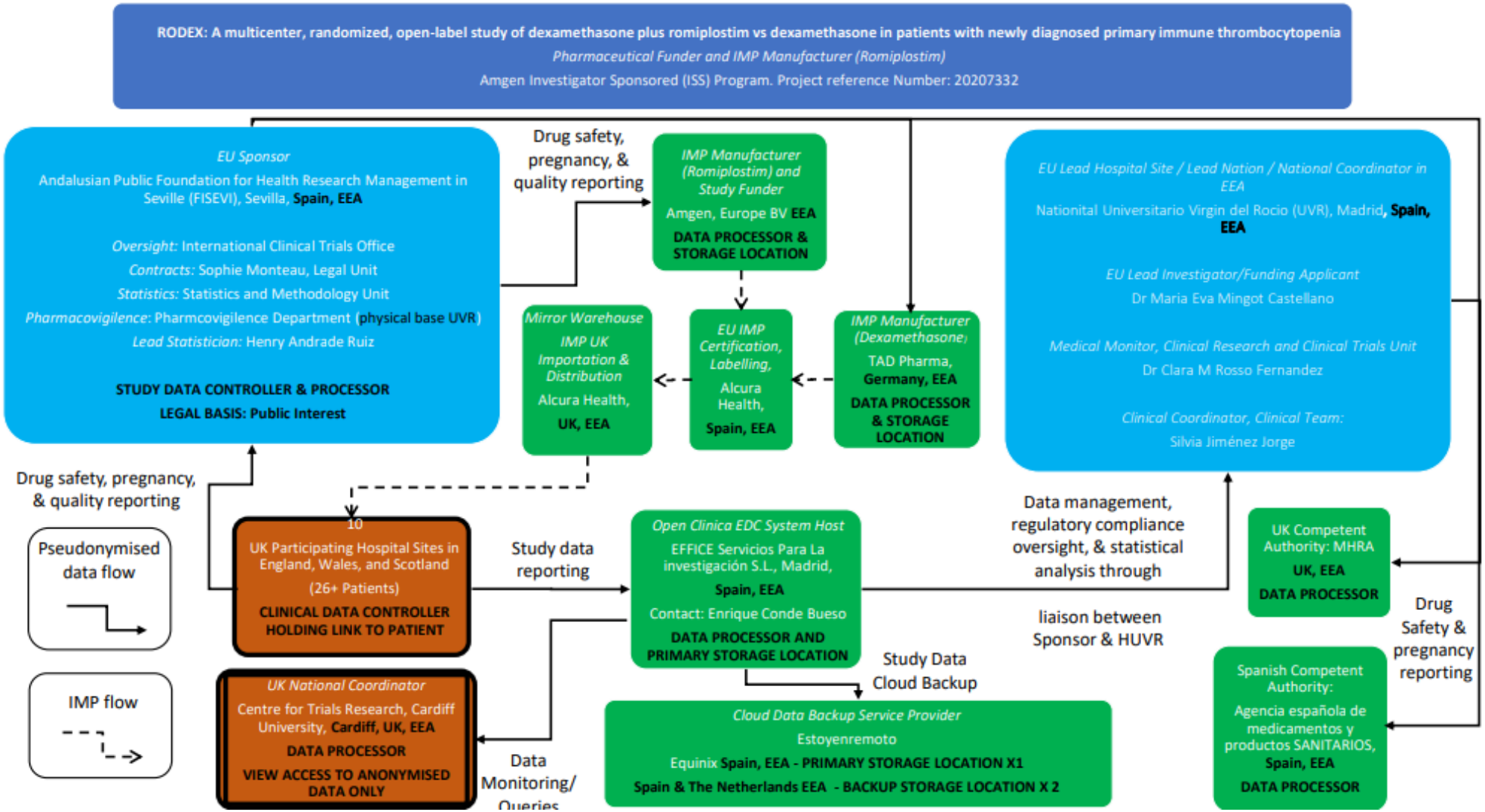
	25) Any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures. 26) Other serious comorbidities at investigator criteria.	
Primary objective	To evaluate the superiority of romiplostim plus dexamethasone vs dexamethasone alone in patients with newly diagnosed primary immune thrombocytopenia (ITP) in terms of sustained response off any ITP treatment (6 months (≥180 days) from treatment cessation, 6mSROT-50) and without WHO grade 2 or more bleeding.	
Secondary objectives	Multiple as described in Main Protocol	
Primary outcomes	To evaluate the difference between study arms in the proportion of patients achieving 6mSROT-50 at 6 months (180 days) from treatment cessation.	
Secondary outcomes	Multiple secondary outcomes as detailed in Main Protocol.	
Investigational medicinal products (IMPs)	**Dexamethasone (DEX) (comparator drug)**	**Romiplostim (ROM) (investigational drug)**
Manufacturer	TAD Pharma, UK	Amgen, UK
EU Certification, Labelling	Alcura Health, Spain	Alcura Health, Spain
UK Import and Distribution	Alcura Health, UK	Alcura Health, UK
Form	Uncoated tablets (4 or 12 per blister pack)	5mL single-use vial of sterile, preservative-free, lyophilised, solid white powder for resuspension
Dose	40 mg daily: **Investigational arm:** X 4 days only in the first cycle and subcutaneous romiplostim weekly (ROM + DEX arm) for up to 12 months **Comparator (DEX arm):** Dexamethasone 40 mg daily x 4 days for up to 3 cycles every 14 to 28 days	Starting dose of 3 mcg/kg calculated on current body weight. Adjusting the following doses according to platelet counts.
Route	Oral taken at home by participant	Subcutaneous injection
Storage	Below 25°C. Protect from light and humidity.	2-8°C. Protect from light.
Routine rescue medication	IVIg, platelet transfusion or prednisone. Tranexamic acid can be used but is not considered a rescue medication (excluded).	

3 Trial summary & schema

3.1 Trial schema/participant flow diagram



3.2 Organogram and data/drug flow diagram



3.3 Trial lay summary

RODEX is investigating Immune Thromobocytopenia (ITP), and an autoimmune disease where the immune system attacks important blood cells called platelets, which are essential for normal clotting. Patients with ITP have reduced numbers of platelets and are at risk of bleeding. A course of corticosteroids (steroids – a man-made version of a hormone the body makes naturally) is recommended as the first line of treatment for adults with newly diagnosed ITP. Most patients with ITP respond to corticosteroids with a rise in platelet count, but improvements are usually temporary and the majority of patients will relapse.

The objective of RODEX is to find out if a two-drug combination of corticosteroids (dexamethasone) plus a medicine called romiplostim is better than dexamethasone alone for first-line of treatment of ITP. Romiplostim is a thrombopoietin-receptor agonist (TPO-RA). Thrombopoietin (TPO) is the natural chemical that the body produces to tell the bone marrow to make more platelets. TPO-RA's are treatments that act like the body's own TPO to increase the number of platelets that are produced.

RODEX will recruit up to 126 adult (≥18 years) patients at up to 30 hospital sites in the European Economic Area (EEA), including Spain and Italy and up to 15 sites and 26+ participants in England, Wales and Scotland, UK. Adult patients will be eligible to take part if they meet the eligibility criteria, including recently diagnosed ITP with a low platelet count and no prior ITP treatment. Participants will be randomly allocated by a computer to receive a course of dexamethasone alone (control arm) or dexamethasone pus romiplostim (investigational arm) and followed up for up to 2 years (screening, day 1, week 8, week 12, month 6, month 12, and end of Study Visit) to find out if dexamethasone plus romiplostim can improve long-term treatment response and avoid bleeding. Study treatments and visits will vary slightly dependent on study arm.

4 Background

RODEX is an international CTIMP study. The lead Nation is Spain. Participants will be recruited in three nations within the EU: Spain, Italy and the UK via three different National Coordinators. Cardiff University is the UK National Coordinator and has delegated the responsible of Trial Management oversight in the UK to the Centre for Trials Research (CTR) within Cardiff University. Global regulatory approvals were in place in Spain and Italy prior to submission of the study to UK regulatory bodies. Refer to current English translation of Main Spanish Protocol for further background information.

5 Trial objectives/endpoints and outcome measures

Refer to Section 2 Synopsis and Section 3.1 for Trial Schema summarising patient flow, study objectives and outcome measures. Refer to Main Protocol for overall trial plan, design and rationale.

6 Risk assessment

The Main Protocol and this UK Protocol Addendum have approval from a UK Research Ethics Committee (REC; Wales REC1) that is legally recognised by the United Kingdom Ethics Committee Authority and the UK Medicines and Healthcare products Regulatory Agency (MHRA). Both documents will be submitted through the relevant permission system for global governance review dependant on the location of the lead UK site e.g. HCRW/HRA.

This clinical trial is to be conducted in compliance with the protocol, the EU Clinical Trial Regulation 536/2014 and Good Clinical Practice. In addition, in the UK, the trial will comply with all relevant UK clinical trial and data protection (General Data Protection Regulations Act 2020) and common law of consent regulations where relevant.

A Trial Risk Assessment and Data Protection Impact Assessment (DPIA) has been completed by the Sponsor to address study to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. A UK-specific Risk Assessment and DPIA has been completed by the UK National Coordinator to address any additional risks specific to delivery of the trial in the UK in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects

- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as a **TYPE B**, where the level of risk is somewhat higher than the risk of standard medical care. A copy of the UK risk assessment may be requested from the CTR. The trial risk assessments will be used to determine the intensity and focus of monitoring activities by the Sponsor and UK National Coordinator.

7 Site and Investigator selection

This trial will be carried out at up to 15 participating sites within the UK (England, Wales and Scotland). The Sponsor will be responsible for site assessment approvals. The UK National Coordinator and CTR will manage, and have oversight for, the UK site set up green light procedure.

All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial.

Before any Site can begin recruitment a Principal Investigator (PI) at each site must be identified and the PI and Site added to the Sponsor's UK insurance policy. The following documents must also be in place and copies sent to the CTR RODEX email account (see contact details on page 4):

- Confirmation of Capacity and Capability (C&C) from R&D department following sharing of local information pack.
- Favourable opinion of host care organisation/PI from Main Ethics committee
- MHRA approval
- Current Curriculum Vitae and Good Clinical Practice (GCP) training certificate of the Principal Investigator (PI)
- Completed Site Staff Delegation Log and Roles and Responsibilities document
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the UK Main and Pregnancy Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper
- A copy of the most recent approved UK GP letter on host care organisation headed paper

- A set of laboratory normal ranges and laboratory certification/accreditation from the host care organisation laboratory being used for analyses
- Returned copy of the Self-Evident Correction Log signed by the PI.
- Pharmacy confirmation that the Site has received the first shipment of IMP prior to opening the site as specified in the Main Protocol
- Executed UK Model Agreement for Non-Commercial Research (mNCA) between UK National Coordinator/Sponsor Legal Representative and Site
- Evidence of Site initiation by the CTR (conducted via teleconference)

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Site PI, lead Research Nurse, and lead Pharmacist as a minimum detailing that the centre is now ready and approved by the UK National Coordinator to recruit participants into the trial. This letter/email must be filed in each site's Investigator Site File (ISF). Along with the written confirmation, the site should receive a study pack holding all the documents required to recruit into and deliver the study.

Occasionally during the study, amendments may be made to the study documentation listed above. The CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the Site to ensure that sites obtain local R&D approval for the new documents.

8 Participant selection– see Spanish Protocol

9 Recruitment, Screening and registration – see Spanish Protocol

10 Withdrawal & lost to follow-up

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial.

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from, the reason for withdrawal, and who made the decision to withdraw, for example patient and/or Clinician and/or Sponsor.

In all instances the event, date of withdrawal, reason(s) for withdrawal, aspect(s) of the trial being withdrawn from, and who made the decision, must be documented by the Site in the relevant section of the EDC System and the participants' hospital record.

For full details of withdrawal criteria, processes for handling withdrawals, lost to-follow up, permitted reasons for withdrawal, and data collection and other reporting requirements following withdrawal, refer to Section 8 of the Main Protocol.

For a summary of withdrawal options and associated actions see Section 9.1 below.

Queries relating to withdrawal of a participant should be forwarded to the CTR study email address in the first instance.

10.1 Summary of Withdrawal Options and Follow-Up Actions

In all cases participants will be followed up following RODEX visit/assessment schedule unless participant also explicitly withdraws their consent to do so, or other reason marked with an asterix (*) below.

Withdrawal From Trial Treatment Intervention	Primary Reason	Decision can be made by			Comments
		Patient	Local Investigator	Sponsor	
	No response - treatment failure		X	X	Withdraw from ROM only, DEX only, or ROM + DEX Participant still followed up following RODEX visit/assessment schedule
	Patient choice	X			
	Adverse Event (AE)		X	X	AE will be followed up until AE resolved/stabilized. Complete and submit SAE notification form if considered an SAE.
	Intercurrent illness or worsening of a chronic condition		X	X	
	Diagnosis no longer ITP		X	X	
	Pregnancy		X		Female participants who become pregnant within 1 month of stopping treatment to be given pregnancy PIS/ICF and asked to provide <u>optional</u> consent for collection of pregnancy data. Complete and submit pregnancy notification form <u>only</u> if optional consent provided.
	Intention to become pregnant	X	X		
	Breastfeeding (lactation)		X		Notify Sponsor/CTR by email. No separate data collection form or consent form to complete.
	Intention to breast feed (lactate)	X	X		
	*Death **		X		Complete death eCRF, and other relevant eCRF up to date of death.
	*Lost-to-follow up **		X		If repeatedly fails to attend scheduled visits and is unable to be contacted by the study site following three telephone call attempts (where possible). Calls must bet documented in medical notes. Complete relevant eCRF up to date of lost-to-follow up.
	Patient non-compliance with treatment schedule		X	X	Report as a patient non-compliance
	Non-compliance with Protocol and/or study procedures		X	X	Report as a study non-compliance

Withdrawal From Other Trial Activities	Primary Reason	Decision can be made by			Comments
		Patient	Local Investigator	Sponsor	
Questionnaires					
SF-36 QOL	Other – e.g. excessive burden	X			Report as a subject non-compliance if not returned
FACTIT QOL		X			
ITP PAQ QOL		X			
ITP BAT		X			
Further study visits/assessments *		X			Report as a subject non-compliance if not attended unless participant deceased or lost-to-follow up
Further non-routine blood sample collection *		X			Report as a subject non-compliance. Any non-routine blood samples collected to provide study assessment data must be destroyed immediately following assessment following local destruction procedure and destruction evidenced in hospital notes and TSF and notified to CTR to meet UK HTA regulatory requirements.

Withdrawal from Data Use	Primary Reason	Decision can be made by			Comments
		Patient	Local Investigator	Sponsor	
Use of data <u>already</u> collected from medical notes/systems for RODEX study purposes	Other	X			Report as a protocol non-compliance. <u>Note:</u> data already entered onto EDC cannot prior to withdrawal will not be destroyed.
<u>Further</u> data collection from medical notes/systems following withdrawal *	Other	X			Report as a protocol non-compliance and stop participant treatment.
Use of data for future research	Other	X			

Withdrawal From Whole trial	Primary Reason	Decision can be made by			Comments
		Patient	Local Investigator	Sponsor	
	Screening failure - eligibility criteria not fulfilled		X	X	Patient can be re-screened once only. This type of withdrawal is not permitted once the patient has been randomised. Eligibility issues identified after randomisation must be reported as a study non-compliance.
	Non-compliance with Protocol and/or study procedures		X	X	Specify reason
	Urgent Safety Measure		X	X	Specify reason
	Early termination of study			X	Specify reason
	Temporary suspension of study			X	Specify reason
	Other	X	X	X	Specify reason

Withdrawal From Provision of mother/child pregnancy reporting data	Primary Reason	Decision can be made by			Comments
		Patient	Local Investigator	Sponsor	
	Other	X			Only if consent provided via UK Pregnancy ICF consent is withdrawn for any reason

11 Trial Intervention

See Spanish Protocol for treatment supply, storage and dosing, concomitant medication, rescue medicine, study treatment stopping and dose adjustment rules, and other trial restrictions, including pregnancy, lactation, breastfeeding, contraception.

11.1 Trial Drug Supplies

Trial drug supply (Romiplostim and Dexamethasone) to UK participating sites will be triggered via the CTR UK green light procedure. Upon receipt of the site set up documentation dossier, enough IMP for full protocol treatment of 4 participants will be provided to the pharmacy at the address provided to CTR. Site will not be activated for recruitment until Site has confirmed receipt of trial IMP. IMP resupply will be upon request by Site as required on an adhoc basis following the Sponsor re-supply procedure.

11.2 Emergency Treatment With Dexamethasone

The use of commercial dexamethasone from UK hospital stocks will be permitted for up to 3 days only following date of trial registration as emergency care whilst study eligibility is assessed and labelled study medication is assigned. Other types of ITP pre-treatment, e.g. prednisolone, are prohibited.

11.3 Self-Administration of Drugs

See Section 7 of the Romiplostim Summary of Product Characteristics (SPC) for instructions for preparing and giving an injection of Romiplostim. The first injection of Romiplostim must be administered by the Site. Sites must ensure that participants have received training in self-administration of Romiplostim and Dexamethasone (table) as per the main Protocol and local hospital procedural requirements, and are comfortable with self-administration, prior to permitting self-administration by the participant at home. The local green light for self-administration must be evidenced in the participants hospital notes.

11.4 IMP Accountability

The CTR will be responsible for IMP accountability and management oversight in the UK via the EDC, remote and/or face-to-face site monitoring as documented in CTR Monitoring Plan, and liaison with drug manufacturers (Amgen and TAD Pharma), certifier (Alcura Health, Spain), importer and distributor (Alcura Health, UK), Site, and Sponsor.

Sites are responsible for documenting local IMP accountability via the EDC following instructions provided by the Sponsor.

11.5 IMP Storage Conditions and Temperature Monitoring

Refer to the Main Protocol for the IMP temperature monitoring and reporting procedure and below for UK storage and monitoring requirements:

IMP	Storage conditions	Site temperature monitoring
Dexamethasone (blister pack of 12 tablets for oral administration)	Below 25°C (as per trial drug label and contrary to SPC guidance - due to recent EU high summer temperatures). In original packaging to protect from light and humidity.	During storage at site via local temperature monitoring.
Romiplostim * (white lyophilised powder for injection) Refer to the Main Protocol for Romiplostim reconstitution guidelines and permitted storage conditions and durations.	2-8°C (fridge). Protected from light.	During transit via return of shipment temperature monitor device. During storage at site via local temperature monitoring.

Temperatures will be logged at site using the RODEX Temperature Log provided in Site Pack where applicable.

Refer to the RODEX IMP Accepted Storage Conditions April 2023 document provided in the Site Pack for permitted storage condition deviations.

Non-permitted temperature deviations will be reported by Site on the RODEX Temperature Deviation Form provided in Site Pack. Forms should be emailed directly to Sponsor Trial Team, copying in the CTR Trial Team.

See Section 12.4 for UK Event Reporting Flow Diagram.

11.6 IMP Quality Complaint Reports

Refer to the Main Protocol for the IMP quality complaint monitoring and reporting procedure.
See Section 12.4 for Uk Event Reporting Flow Diagram.

12 Samples, Visits, Assessments, Questionnaires and Health Resource Utilisation

For full details refer to Section 10. Study Schedule of Main Protocol. Participants will remain on study and in follow up for up to two years.

12.1 Study visits, assessments, and samples

No urine samples will be collected above and beyond those collected for UK routine care.

Routine blood sample collections, visits, and assessment requirements vary for the UK RODEX patient cohort dependent on local hospital differences in ITP-treatment practices permitted under UK NICE ITP Treatment guidance: https://bnf.nice.org.uk/treatment-summaries/immune-thrombocytopenic-purpura/. The number and frequency of study-specific visits for the collection and assessment of RODEX trial-specific blood samples will be marginally higher than routine care at most, and vary across different, UK participating sites.

SOECAT costs associated with routine and research visits, assessments and samples are based on local practice at the lead UK participating site (University Hospitals Bristol and Weston NHS Foundation Trust); collection of up to three new blood samples above and beyond routine care from participants assigned to Arm A (ROM+DEX) only during weeks 9-15 for clinical trial assessment purposes only.

Local differences to the lead UK Site procedure must be documented on the site registration form and discussed with the UK National Coordinator prior to site set up and site green light approval.

All research and/or routine samples will not be transferred outside of the collecting host NHS organisation and will be destroyed immediately following analysis following local policies and procedures.

Responsibility for sample collection resides with the Sponsor. For avoidance of doubt, the research will be registered on the UK National Coordinator's Human Tissue Authority (HTA) Register (Holding Number: 702).

12.2 Quality of Life Questionnaires

Three validated quality of life questionnaires (SF-36, FACIT-Fatigue Scale, and ITP Patient Assessment Questionnaire (ITP-PAQ), will be completed by each participant at five different time points from baseline to end of treatment as specified in the Main Protocol and for study purposes only. Questionnaires will be provided to participants by site as PDFs. Data entered on completed questionnaires will be remotely entered on the EDC System by Sites.

12.3 Health Resource Utilisation (HRU)

Data associated with health resource utilization will be collected from hospital records and entered on the EDC by Sites, supported by discussion with patient at trial visits where applicable.

12.4 Bleeding Events

Bleeding will be assessed by Site at every visit. Events will be assessed using WHO grading. ITP-specific bleeding using the ITP-BAT tool at the timepoints specified in the Main Protocol. All bleeding data will be entered remotely on the relevant section of the EDC System by Sites.

12.5 Patient Travel Expense Claims

Participants may claim travel expenses incurred for any study visit deemed by the site PI to be above and beyond local routine care as pre-agreed with the National Coordinator during site set up and in compliance with the reimbursement criteria, limits and process specified in the mNCA.

13 Safety Reporting

Refer to Main Protocol for full pharmacovigilance definitions and reporting procedures. Safety reporting responsibilities of individual parties are summarised below.

The site is responsible for assessing all locally incurred UK safety and quality events and reporting them directly to the Sponsor at the email address specified in the Main Protocol:

Email address for reporting safety and quality complaint events:

Unidad de Investigación Clínica y Ensayos Clínicos

Hospital Universitario Virgen del Rocío

Dpto. Farmacovigilancia

Email: pv.uicec.fisevi@juntadeandalucia.es

Avda. Manuel Siurot S/N

41013. Sevilla

Tel.: +34 955 01 34 14

Fax: +34 955095338

The Sponsor has delegated overall responsibility for centrally documenting SAEs and reporting of safety events to the Pharmacovigilance Department, HUVR, Spain.

The Sponsor has delegated some UK safety reporting activities to the CTR as specified below and documented in the CTR UK RODEX Safety Management Plan.

13.1 Reference Safety Information (RSI)

Reference Safety Information (RSI) will be reviewed regularly by the Sponsor. Refer to the main Protocol for a list of documents and sections to be used as the RSI for the purpose of site assessment of safety events. Refer to Amgen Risks and Discomforts Letter and document for recent manufacturer's information about risks and discomforts associated with Romiplostim.

13.2 SAE and Quality Complaints Reporting

See Main Protocol Section 11 for SAE and Quality Complaint reporting procedures.

Serious Adverse events (SAE) should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and reported using the RODEX SAE Reporting Form.

The PI (or delegated medically qualified doctor from the trial team) should sign and date the form following procedures specified in the Main Protocol to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

All adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including 30 days after the participant receives their last dose of the IMP. Serious adverse reactions (SARS; such as long term side effects of trial treatment under investigation) should continue to be reported until the end of follow up as defined in the protocol.

The participant will be identified on the SAE form by t**rial number, age (year/month/day), age group, full date of birth and (if applicable) full date of death only**. The participant's name (or any other personal identifiers) should not be used on any correspondence with the Sponsor and/or CTR, i.e. reported in pseudonymised format. The participant will be identified to the CTR via trial number only.

Minimum reporting data fields and reporting timeframe restrictions are specified in the Main Protocol.

Sites must respond to and clarify any queries raised by the Sponsor on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, drug companies may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

13.3 Safety Reports

13.3.1 SARs & SUSARs

Investigator reports of suspected SARs will be reviewed immediately by the Medical Monitor or suitable delegate(s) appointed by the Sponsor as specified in the Main Protocol. Those that are identified as SUSARs will be notified by FISEVI Pharmacovigilance department directly to the international European Medicines Agency (EMA) via the Eudravigilance System (EVWEB), and to the

relevant drugs company where applicable. The Sponsor will forward SUSAR events in UK Participants to the CTR for onward reporting by the CTR to the MHRA via EU Individual Case Safety Report (ICSR) System.

13.3.2 Annual DSUR, ISR and Final Report

Safety reports will be aggregated and drafted by the Sponsor.

A list of all SARs (expected and unexpected) will be reported annually to the CTR by the Sponsor for forwarding by the CTR to the MHRA and REC, in the form of a single Development Safety Update Report (DSUR) covering both trial IMPs. This report must be submitted to UK regulatory bodies within 60 days of the anniversary of the original Agencia Espanola de Medicamentos U Productos Sanitarios (AEMPS) approval date.

The Sponsor will report a list of all SARs (expected and unexpected) and any other safety recommendations to the CTR for notification to all UK PIs annually throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR) which will be authored by the Sponsor.

The Sponsor is responsible for uploading the end of trial summary results to EudraCT as per the commission's guidelines on posting and publication of result-related information. All SAEs and AEs will be CTCAE coded or MedDRA coded to support upload.

13.3.3 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial will be notified by the Sponsor to the CTR for onward notification to the MHRA and REC immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to the RODEX UK Safety Management Plan and Main Protocol.

13.3.4 Pregnancy Reporting

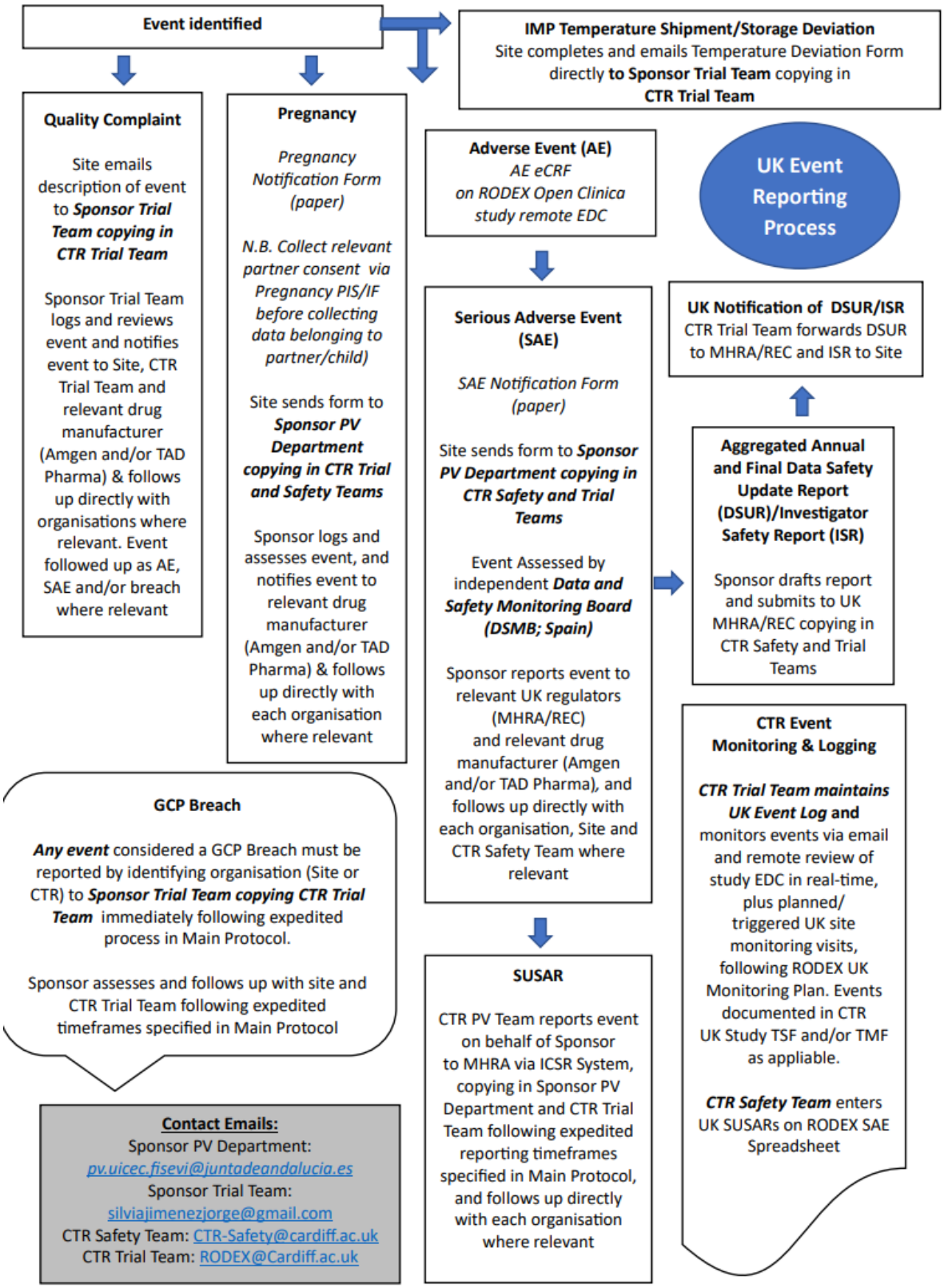
Despite strict exclusion criteria around pregnancy, breast feeding and contraception and the anticipated low number of UK participants, there remains a very low risk that a participant (or for male participants, their female partner) will become pregnant during the study. If a pregnancy occurs, the participant (or their female partner where applicable), will be asked to provide **optional** consent via the study UK Pregnancy PIS/ICF for safety reporting of pregnancy data to the Sponsor and drug company (Amgen and/or TAD Pharma) where applicable.

Reported data may include confidential patient data belonging to the pregnant mother, and her unborn fetus and/or born child (including sex, date of birth and date of death).

This data will be collected and stored for a minimum of 25 years by the Sponsor in the interest of clinical trial regulatory compliance, and indefinitely by the drug manufacture under the mother's own consent, and parental consent provided on behalf of the born child where applicable, provided via the Pregnancy ICF.

The CTR will monitor for events of reporting confidential data belonging to a born child throughout the study, and liaise with the Sponsor to ascertain at the end of the participant follow up phase if/when there is a requirement for an application for CAG for CAGs251 and/or Scottish equivalent consent exemption as applicable (and continued REC approval) to support retention of data collected during childhood from a child born in England, Wales or Scotland beyond the date said child(ren) reach maturity to adulthood (age 16 years or over).

13.4 UK Event Reporting Flow Diagram



14 Statistical considerations

14.1 Randomisation

This is a randomised study. Participants will be randomised to one of the two trial arms by site via the computerised EDC System following consent, registration and confirmation of eligibility. A paper backup randomisation procedure will be used if the EDC System is inaccessible for any reason. The Sponsor is responsible for monitoring randomisation.

14.2 Blinding

This is an open label study. The participant and their treating team and GP will know which trial arm the participant has been assigned to. The study statistician and suitable delegate(s) responsible for analysis will be blinded to the results until the study analysis has been conducted in the interest of bias prevention.

14.3 Analysis

Study analysis will be delegated by the Sponsor to the Statistics and Methodology Unit, HUVR, Spain.

15 Data Management

As described in the Main Protocol, trial data, including registration, randomisation, consent and withdrawal data, will be collected via remote data entry by site into the study-specific Electronic Data Capture (EDC) System using the Open Clinica software platform.

The Sponsor has delegated development, hosting, and management of the EDC System to EFFICE Servicios Para La investigación S.L., Madrid, Spain.

The EDC will be accessed at the following web address:

https://www.efficecrf.com/OpenClinica

Individual log-in details will be provided by Effice to the CTR and/or Site as required, e..g upon site activation.

A study-specific Open Clinica Investigator Guideline, inclusive of login, support and user instructions, will be provided to sites prior to activation to recruitment and data capture.

The CTR will liaise with UK sites, EFFICE, and the Sponsor to ensure data is completed, queried and amended as per the requirements of the trial and in a timely manner via restricted access to the EDC System.

The CTR UK Data Management Plan and Monitoring Plan, and agreement between Sponsor and National Coordinator, will document CTR monitoring activities and responsibilities.

For further information about data management refer to the Main Protocol.

16 Translational research or sub-trial – not applicable

17 Protocol/GCP non-compliance

The CTR RODEX SOP List will document if/when CTR and/or Sponsor SOPs will be followed to support delivery of the study in the UK. A CTR SOP exemption form will be completed where applicable.

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of GCP to the CTR in writing as soon as they become aware of it using the relevant form provided by the Sponsor, for onward reporting by the CTR to the Sponsor.

18 End of Trial definition

The end of the trial is defined as the date of final data capture to meet the trial endpoint. In this case end of trial is defined as the date of the hard data lock of the EDC, i.e. date of last visit and data capture.

The CTR will, on behalf of the UK National Coordinator and Sponsor, notify the MHRA and main REC of the end of the trial within 90 days of its completion or within 15 days if the trial is terminated early and submit the final REC and MHRA reports within UK regulatory reporting timeframe requirements.

19 Archiving

The CTR, on behalf of the UK National Coordinator and Sponsor, will be responsible for archiving UK trial documentation. Documents specifically relating to the approval and conduct of the trial in the UK are considered essential UK TMF documents and will be archived at an approved external storage facility by the UK lead organisation for a minimum of 25 years.

A copy of the UK TMF will be provided to the Sponsor following study closure in the UK as specified in the agreement between the Sponsor-UK National Coordinator.

The Principal Investigator at UK sites is responsible for archival of the local study ISF at site on approval from the CTR on behalf of the UK National Coordinator and Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

20 Regulatory Considerations

The Sponsor is responsible for EU regulatory submissions. Refer to Main Protocol for EU regulatory details.

The Sponsor has delegated the role of managing UK regulatory submissions to UK National Coordinator and CTR.

This trial has Clinical Trials Authorisation (CTA) from the UK Competent Authority (MHRA).

The Main Protocol and this UK Protocol Addendum have approval from a Research Ethics Committee (REC) that is legally "recognised" by the UK Ethics Committee Authority for review and approval, and will be submitted through the relevant permission system for global governance review dependant on the location of the lead site e.g. HRA (England) and devolved equivalents (Wales and Scotland).

Approval will be obtained from the host care organisation in the UK who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

20.1 Data Protection

This trial is being conducted in the UK in compliance with the UK Data Protection Act 2022, GDPR 2020, and the Common Law of Confidentiality legislation.

The legal basis for the collection, transfer and retention of study data from UK participants will be 'public interest'.

Written informed consent for study participation, treatment and the transfer of patient confidential data, will be provided by the participant by completion of the study PIS/ICF.

The Sponsor (FISEVI) will act as the sole data controller under GDPR 2020 and EU equivalent legislation.

Participating Sites will act as the data controller for patient confidential data sourced at Site from local clinical records.

The study teams responsible for clinical trial oversight, statistical analysis, and pharmacovigilance based at HUVR, the National Coordinator (Cardiff University), the UK CTU (CTR), UK participating sites, the EDC service provider (EFFICE), EDC cloud back up service provider (Estoyenremoto), drug manufacturers (Amgen and TAD Pharma), drug distributor (Alcura Health, UK), and Spanish and UK national competent and regulatory bodies will all act as data processors for various sub-sets of data collected from participants recruited in the UK devolved nations.

A full list of these data controllers and processors is provided to participants in the UK PIS/ICF.

Refer to Section 3.2. (Organogram and data flow/drug diagram) of this Protocol Addendum for further details of data flow to and from UK participants, Sites, and individual UK and non-UK data processors, and the overall trial data controller (Sponsor).

Participants will be identified by the Sponsor by a set of pseudonymised identifiers referenced in the PIS/ICF.

The CTR and UK National Coordinator will only be able to identify participants in the EDC and communications with Sponsor, site and other study partners by their unique study Patient ID number assigned at registration by the Sponsor and UK site via the central study EDC system.

The CTR and UK National Coordinator will act on behalf of the Sponsor to preserve UK participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained.

Data will be stored in a secure manner following Sponsor, National Coordinator, CTR and other partner organisations' data protection policies, procedures and guidelines and in accordance with the aforementioned UK Data Protection legislation, and the Sponsor and CTR study-specific Risk Assessment DPIA.

20.2 Indemnity

- Non-negligent harm: This trial is an EU academic, investigator-led and designed trial, with UK National Coordinator responsibility delegated to Cardiff University and UK Trial Management coordinated by the CTR. The UK Chief Investigator (CI), local Principal Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

- Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this trial. The UK Sponsor does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The UK Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the UK Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the UK Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.
- Sponsors EU Trial Insurance Policy: Company - HDI Global SE España; Policy Number: 08057795-30068. Full details provided in the Main Protocol.
- Sponsor UK Trial Insurance Policy: Company – HDI; Policy Number: 390-76695094-30017.
- UK National Coordinator Insurance Policy: Company – U.M. Association Ltd ; Policy Number: CT Q1101.
- NHS indemnity is not applicable to this study.

20.3 Trial sponsorship

The Sponsor, UK National Coordinator and delegated UK CRO are detailed on page 2 of this UK Protocol Addendum. Delegated responsibilities as specified in the UK mNCA will be assigned by the UK Sponsor to UK sites taking part in this trial.

The CTR, on behalf of the UK National Coordinator, shall be responsible for ensuring that the trial is performed in the UK in accordance with the following:

- Main RODEX Protocol
- UK RODEX Protocol Addendum (this document)
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments
- Conditions and principles of Good Clinical Practice (GCP)
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research
- The UK DPA 2022, GDPR 2020 and Common Law of Confidentiality and subsequent amendments

- Other EU and UK regulatory requirements as appropriate

21 Trial management

Details of the RODEX Trial Management Group, Independent Data Monitoring Committee, Trial Steering Committee, and other types of oversight where relevant are provided in the Main Protocol. No additional oversight will be provided in the UK.

22 Quality Control and Assurance

22.1 Monitoring

The Sponsor and UK National Coordinator clinical trial risk assessments have been used to determine the intensity and focus of central and on-site monitoring activity in the RODEX trial. Central monitoring of UK data and data return rates will be employed and are documented in main trial monitoring plan.

The CTR will be responsible for regular central and site monitoring in the UK. The CTR will employ low level central monitoring via remote view of the study EDC database. The CTR will employ moderate level site monitoring of UK sites. Full details, including frequencies and format (remote and/or in person), of planned and triggered UK site monitoring and central monitoring will be specified in the CTR UK Site Monitoring Plan.

Investigators are required to agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. This process is described in the study participant consent documentation and the Main Protocol. Findings generated from central monitoring will be shared with the EU and UK Sponsor(S), EU and UK CI(s), and local PI & R&D as required to meet EU and UK clinical trial regulatory requirements and specified in the Main Protocol.

22.2 Audits & Inspections

The UK CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/ IRB review, by relevant EU and UK regulatory bodies, Sponsors and CROs (inclusive of the CTR) and providing direct access to source data/documents for these organisations for EU and UK clinical trial regulatory purposes as specified in the Main Protocol.

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/ IRB review, and regulatory inspection(s), providing direct access to source data / documents.

The site must inform the CTR of any MHRA inspections.

23 Public Involvement and Engagement

Members of the public have reviewed the study where required under Sponsor and funder procedures and policies. The CTR Study Adoption Group includes a lay member and has reviewed and adopted the study into the CTR study portfolio. The Spanish and UK REC review panels will include members of the public.

24 Publication Policy

All publications and presentations relating to the trial will be authorised by the Trial Management Group and Sponsor following publication details provided in the Main Protocol.

UK sites must follow any publication restrictions specified in the UK mNCA between UK Sponsor and Site.

Study results will be uploaded to relevant trial databases and disseminated to participants in the UK via the UK sites and/or the CTR-hosted study website (https://www.cardiff.ac.uk/centre-for-trials-research) as relevant.

25 Milestones

The study opened to recruitment in the lead site (Spain) December 2022. The last study patient is anticipated to be recruited by the first quarter of 2024. The 12 month treatment phase will be followed by a non-interventional 12 month follow-up period which will continue for up to one year after the last participant completes protocol treatment. Each participant will remain on study for up to 24 months.

The UK Sponsor aims to open and close the study to recruitment in the UK in 2023 and 2024 respectively, and to complete UK patient follow up by 2025.

A study calendar describing overall study milestones is provided in the Main Protocol.

26 References

- Common Terminology Criteria for Adverse Events (NCI CTC) V5.0
- WHO / ECOG Performance Status
- Dexamethasone trial drug label
- Romiplostim trial drug label
- Dexamethasone SPC
- Romiplostim SPC
- Romiplostim IB
- Amgen NPLATE Risks and Discomforts Letter 21/11/2022
- Amgen NPLATE Risks and Discomforts Version 9.0 08/11/2022
- RODEX Temperature Log
- RODEX Temperature Deviation Form
- RODEX Quality Complaint Reporting Form
- RODEX IMP Accepted Storage Conditions April 2023
- UK PIS/ICF
- UK Pregnancy PIS/ICF
- RODEX Electronic Data Capture (EDC) System
- RODEX EDC Data Collection eCRF
- RODEX SAE Data Collection Form
- RODEX Pregnancy Reporting Form
- ITP-BAT
- SF36 Quality of Life Questionnaire
- FACIT Quality of Life Questionnaire
- ITP PAQ Quality of Life Questionnaire
- Spanish RODEX Risk Assessment Form/Data Protection Impact Assessment (RAF/DPIA)
- CTR UK RODEX RAF/DPIA

- Spanish RODEX Monitoring Plan
- CTR RODEX Monitoring plan
- Spanish RODEX Data Management Plan
- CTR RODEX Data Management Plan
- Spanish RODEX Safety Management Plan
- CTR RODEX Safety Management Plan
- UK Site Pack
- UK Site Registration Form