# Clinical Study Protocol

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| **Protocol Title: RENAISSANCE** - A multi-centre, non-interventional study of **RE**lugolix as a**N**drogen-depriv**A**tion therapy **I**n patient**S** with advanced hormone-**S**ensitive prostate c**ANCE**r | |
| **Short Title:** A non-interventional study of relugolix in advanced hormone-sensitive prostate cancer. | |
| **Product:** Relugolix 120mg film-coated tablets | **Document Type:** Clinical Study Protocol |
| **Protocol Number:** ACC-RNI-001 | **Version:** 1.0 |
| **Version Date:** 19-Feb-2024 | **Document Status:** Effective |
| **Submission: N/A** | |
| **Sponsor Name:** Accord Healthcare<br>**Legal Registered Address:** 319 Pinner Road Harrow HA1 4HF, UK | **CRO Name:** PHARMExcel<br>**Legal Registered Address:** 26 Bridge Road, Welwyn Garden City, AL7 1HL, UK |
| **GCP Compliance:** This study will be conducted in compliance with the protocol, Good Clinical Practice, and all other applicable regulatory requirements. | |

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## Contents

# 1. Responsible parties

**Abbreviated title:** RENAISSANCE

**Study number:** ACC-RNI-001

**Date of protocol**: 01/02/2023

**Version:** Version 1.0

**Detailed title**: A multi-centre, non-interventional study of RElugolix as aNdrogen-deprivAtion therapy In patientS with advanced hormone-Sensitive prostate cANCEr.

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# 2. List of Abbreviations

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|---|---|
| ADR | Adverse Drug Reaction |
| ADT | Androgen-Deprivation Therapy |
| AE | Adverse Event |
| BW | Body weight |
| CRF | Case report form |
| CRO | Contract research organization |
| CTC | Common toxicity criteria |
| CV | Cardiovascular |
| ECOG PS | Eastern Cooperative Oncology Group (ECOG) Performance Status |
| EDC | Electronic data capture |
| EOS | End of study |
| GCP | Good Clinical Practice |
| GnRH | Gonadotropin-releasing hormone |
| HCP | Healthcare Professional |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| LHRH | Luteinizing Hormone-Releasing Hormone |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MSL | Medical Science Liaison |
| PCa | Prostate cancer |
| PI | Principal Investigator |
| PSA | Prostate Specific Antigen |
| SAP | Statistical Analysis Plan |
| TMF | Trial master file |
| TNM | Tumor Nodes Metastases |

# 3. Abstract

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| **Name of Sponsor** | Accord Healthcare Ltd |
| **Name of Finished Product** | Orgovyx® |
| **Name of Active Ingredients** | relugolix |
| **Title** | **RENAISSANCE** - A multi-centre, non-interventional study of **RE**lugolix as a**N**drogen-deprivation therapy **I**n patient**S** with advanced hormone-**S**ensitive prostate c**ANCE**r |
| **Study number (internal)** | ACC-RNI-001 |
| **Phase of development** | Phase IV (non-interventional post approval study) |
| **Rationale and background** | On April 29, 2022, the European Commission (EC), and on June 17, 2022, the United Kingdom (U.K.) Medicines and Healthcare products Regulatory Agency (MHRA), approved ORGOVYX as the first oral androgen deprivation therapy for advanced hormone-sensitive prostate cancer in the European Union (EU) and U.K.<br><br>The approval was based on the pivotal study MVT-601-3201/HERO, a phase 3, multi-national, randomized, open-label, parallel group study.<br><br>Relugolix real-world evidence of treatment persistence and combination therapy with other prostate cancer medications (e.g., androgen receptor agents and chemotherapy) are areas where additional data are desired, specifically from Europe.<br><br>The study is designed to better understand the actual experience of patients with prostate cancer treated with relugolix by collecting data on treatment patterns, effectiveness, persistence and adherence. Patients will be followed prospectively for up to one year from the date of signed informed consent (enrolment) in order to ascertain patient outcomes for this time period. |
| **Research question and objectives:**<br>**-Primary objective**<br>**-Key secondary objectives**<br>**-Other secondary objectives**<br>**-Exploratory objectives**<br>**-Safety** | The goal of this study is to generate real word evidence from Europe about the population, effectiveness, and persistence of relugolix treatment in patients with advanced hormone-sensitive prostate cancer and their clinical course during treatment.<br><br>**Primary objectives**<br><br>To describe the effectiveness of relugolix in patients with prostate cancer in a real-life setting,<br><br>**Secondary objectives**<br><br>• To describe patient demographics and clinical characteristics of patients with prostate cancer who commence treatment with relugolix. |

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| | • To describe treatment persistence including reasons for changes to and from relugolix treatment.<br>• To describe concomitant prostate cancer treatment received with relugolix.<br>• To understand the progression of prostate cancer during treatment with relugolix including clinical course and disease progression, mortality and comorbidities.<br>• To characterize the safety of patients with prostate cancer treated with relugolix. |
| **Methods (study design/interventions/duration of treatment and follow-up)** | This European, multicentric, prospective cohort study (i.e. non-interventional) will be conducted in patients with advanced hormone-sensitive prostate cancer who are initiating treatment with relugolix with a planned duration of treatment of at least twelve months.<br><br>Patients will undergo clinical assessments and receive standard medical care as determined by the patient's investigator in a real-world practice setting. Patients will not receive any experimental intervention or treatment as part of their participation in this study.<br><br>No mandatory visits, tests, or clinical assessments are required for this study.<br><br>All visits will be scheduled and conducted according to the clinical site's routine clinical practice. Data will be extracted from the medical records and entered into the electronic data capture (EDC) following clinic visits. Sites will be encouraged to extract data 3 times. To capture data on healthcare encounters that occur outside of the setting of the investigator, secondary data will be obtained electronically and imported into the study database on an as needed basis.<br><br>Physicians are free to add or withdraw any medication. Relugolix or any other treatment will not be provided or paid for by Accord Healthcare. Evaluations and testing are as per routine care will not be provided or paid for by Accord Healthcare.<br><br>Patients will be followed prospectively for up to one year from the date of signed informed consent (enrolment) in order to ascertain patient outcomes for this time period. Follow-up will end with withdrawal of consent, loss to follow-up, death, or end of study data collection, whichever comes first. |

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| **Population (main criteria for inclusion/exclusion)** | Study investigators will invite prospectively and consecutively at sites all patients who meet study eligibility criteria to enroll until the target number of patients are enrolled in order to provide a heterogenous patient population.<br><br>**Inclusion Criteria**<br><br>Subjects are eligible to be included in the study only if all the following criteria apply:<br><br>1 Patient who had voluntarily signed and dated the informed consent form.<br>2 Male patients aged 18 years or older.<br>3 Patients who had histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate described in the patient's file.<br>4 Patients deemed eligible for androgen-deprivation therapy with relugolix prescribed as part of standard clinical practice.<br>5 Patient who has agreed with the investigator the initiation of relugolix, per the investigator's decision, prior to enrollment into the study.<br>4 Intended duration of androgen-deprivation therapy of at least twelve months.<br><br>**Exclusion Criteria**<br><br>Any potential subject who meets any of the following criteria will be excluded from participating in the study:<br><br>1 Patient unable to provide informed consent.<br>2 History of surgical castration.<br>3 Intended duration of androgen-deprivation therapy of less than 12 months.<br>4 Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the product information.<br>5 Patient who has already received or is currently receiving relugolix.<br>6 Participants who are not treated in line with current Summary of Product Characteristics for relugolix. |

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| **Total duration of the study** | Patient recruitment: 1 year<br>Maximum patient follow-up in the study: 1 year<br>Total duration: 2 years |
| **Variables:** | • Demographics (country, age, ethnicity)<br>• Baseline clinical characteristics (ECOG PS, baseline disease stage, location of metastases, baseline PSA level / testosterone, prior prostatectomy / radiotherapy / other local intervention, prior ADT, most recent ADT, concomitant medications for PCa, CV comorbidities/risks)<br>• Medical history of prostate cancer (date of diagnosis, cTNM at diagnosis, Gleason, PSA, disease stage)<br>• Relugolix data (date of initiation, reason, posology, interruption with the duration and the reason, date of discontinuation and reason)<br>• Disease evolution during the follow-up (disease state, TNM, PSA, testosterone, interventions)<br>• Concomitant medications for prostate cancer (name of the drug, date of initiation/discontinuation, posology, reason)<br>• Safety (all AE, date, causality, severity) |
| **Data sources** | Data will be extracted from the patient's medical records by site personnel. Once written informed consent has been obtained, study site personnel will complete the data collection at enrolment and throughout the study period for each patient. Follow-up data for patient visits will be recorded in the patient chart in accordance with the clinical site's standard of care or clinical judgment. |
| **Study size** | 300 patients over 6 countries (UK, France, Germany, Italy, Spain, Romania) |
| **Data analysis** | The primary goal of this study is to establish a database of clinical data from patients with prostate cancer treated with relugolix in a real-world practice setting that will characterize treatment patterns for prostate cancer and associated effectiveness and treatment persistence.<br>As such, no formal hypotheses will be tested in this study. |

# 4. Amendments and updates

| **DOCUMENT HISTORY** | | |
|---|---|---|
| **Version** | | **Changes** |
| Version 1.0 | 19/02/2024 | • N/A |

# 5. Milestones

| Milestones | Planned date |
|---|---|
| Start of data collection (First Patient In) | Q2-Q3 2024 |
| End of recruitment (Last Patient In) | Q2-Q3 2025 |
| End of follow-up (Last Patient Last Visit) | Q2-Q3 2026 |
| Study report | Q3-Q4 2026 |

# 6. Background and Rationale

Prostate cancer is the second most common cancer in men worldwide, with over 1.2 million cases and 358,000 deaths annually (Bray et al. 2018). Advanced prostate cancer can encompass a variety of stages or clinical aspects of prostate cancer, ranging from extracapsular extension confined to the pelvis to widely disseminated metastatic disease. Androgen deprivation therapy (ADT) has been the foundation of systemic treatment for men with advanced prostate cancer for more than 70 years [Kreis, 1995].

Gonadotropin-releasing hormone (GnRH) receptor agonists (i.e., long-acting leuprolide acetate, triptorelin, goserelin depot injections) have been the most frequently used modality of ADT for the past 20 years, with most of the data and evidence used to guide clinical use and guidelines for ADT built upon leuprolide. One major disadvantage of using a GnRH receptor agonist to suppress testosterone is the initial stimulation of the hypothalamus-pituitary-gonadal axis that occurs prior to desensitization, which lasts between one and three weeks. This results in an initial rise in luteinizing hormone (LH) and follicle stimulating hormone (FSH), which in turn results in a testosterone surge, and in some men, an increase in clinical symptoms, including increased bone pain, spinal cord compression, pathologic fracture, bladder outlet obstruction, and even death [Oh, 2010].

More recently, GnRH receptor antagonists have been approved for clinical use; relugolix (Orgovyx®), the first oral GnRH receptor antagonist, was approved on 29 April 2022 by the European Medicines Agency (EMA).

Relugolix (previously known as T-1331285, TAK-385 and RVT-601, also known as MVT-601) is an orally active, nonpeptide, GnRH receptor antagonist developed as a 120-mg daily dose (after a loading dose of 360 mg) to induce sustained testosterone suppression to levels < 50 ng/dL for the treatment of men with advanced prostate cancer. In the pivotal study MVT-601-3201/HERO, a phase 3, multi-national, randomized, open-label, parallel group study to evaluate the efficacy and safety of oral daily relugolix 120 mg (after a loading dose of 360 mg) in patients with androgen-sensitive advanced prostate cancer who required at least one year of continuous androgen-deprivation therapy. Three groups of patients were evaluated: men with biochemical or clinical relapse after local primary therapy, men with newly diagnosed hormone-sensitive metastatic prostate cancer, and men with advanced localised disease unlikely to be cured by local primary intervention with either surgery or radiation with curative intent. The HERO study assessed patients through 48 weeks, and measured testosterone suppression as the primary endpoint starting at day 29 through the end of the treatment period. Real-world evidence of treatment persistence and combination therapy with other prostate cancer medications (e.g., androgen receptor agents and chemotherapy) are areas where additional data are desired, specifically from Europe.

This cohort study will be conducted in patients who are initiating treatment with relugolix. The decision to initiate treatment with relugolix should be made prior to study enrolment.

The study is designed to better understand the actual experience of patients with prostate cancer treated with relugolix by collecting data on treatment patterns, effectiveness, persistence and adherence. Patients will be followed prospectively for up to one year from the date of signed informed consent (enrolment) in order to ascertain patient outcomes for this time period.

Follow-up will end with withdrawal of consent, treatment discontinuation, loss to follow-up, death, or end of study data collection, whichever comes first. The data from this study will enable the evaluation of experience and outcomes, which is not possible in a traditional clinical trial due to the limitations of a selected population that may not be representative of actual patient results.

The prospective design enables capturing of important characteristics of patients with prostate cancer at baseline, and then provides longitudinal follow-up to collect information on effectiveness, treatment patterns, and treatment adherence/persistence, as well as safety outcomes.

# 7. Research Question and Objectives

The goal of this study is to generate real word evidence from Europe about the population, effectiveness, and persistence of relugolix treatment in patients with advanced hormone-sensitive prostate cancer and their clinical course during treatment.

**Primary objectives**

To describe the effectiveness of relugolix in patients with prostate cancer in a real-life setting,

**Secondary objectives**

To describe patient demographics and clinical characteristics of patients with prostate cancer who commence treatment with relugolix.

To describe treatment persistence including reasons for changes to and from relugolix treatment.

To describe concomitant prostate cancer treatment received with relugolix.

To understand the progression of prostate cancer during treatment with relugolix including clinical course and disease progression, mortality and comorbidities.

To characterize the safety of patients with prostate cancer treated with relugolix.

# 8. Research methods

## 8.1. Study Design

This European, multicentric, prospective cohort study (i.e. non-interventional) will be conducted in patients with advanced hormone-sensitive prostate cancer who are initiating treatment with relugolix with a planned duration of treatment of at least twelve months.

The study is designed to characterize effectiveness, persistence, and the safety profile of relugolix as androgen-deprivation therapy.

## 8.2. Study Population

Study investigators will invite prospectively and consecutively at sites all patients who meet study eligibility criteria to enroll until the target number of patients are enrolled in order to provide a heterogenous patient population.

**Inclusion Criteria**

Subjects are eligible to be included in the study only if all the following criteria apply:

1 Patient who had voluntarily signed and dated the informed consent form.

2 Male patients aged 18 years or older.

3 Patients who had histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate described in the patient's file.

4 Patients deemed eligible for androgen-deprivation therapy with relugolix prescribed as part of standard clinical practice.

5 Patient who has agreed with the investigator the initiation of relugolix, per the investigator's decision, prior to enrollment into the study.

4 Intended duration of androgen-deprivation therapy of at least twelve months.

**Exclusion Criteria**

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1 Patient unable to provide informed consent.

2 History of surgical castration.

3 Intended duration of androgen-deprivation therapy of less than 12 months.

4 Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the product information.

5 Patient who has already received or is currently receiving relugolix.

6 Participant who is not treated in line with current Summary of Product Characteristics for relugolix.

## 8.3. Study Procedures

Patients will undergo clinical assessments and receive standard medical care as determined by the patient's investigator in a real-world practice setting. Patients will not receive any experimental intervention or treatment as part of their participation in this study.

No mandatory visits, tests, or clinical assessments are required for this study.

All visits will be scheduled and conducted according to the clinical site's routine clinical practice. Data will be extracted from the medical records and entered into the electronic data capture (EDC) following clinic visits. Sites will be encouraged to extract data at least 3 times. To capture data on healthcare encounters that occur outside of the setting of the investigator, secondary data will be obtained electronically and imported into the study database on an as needed basis.

Physicians are free to add or withdraw any medication. Relugolix or any other treatment will not be provided or paid for by Accord Healthcare. Evaluations and testing are as per routine care, and will not be provided or paid for by Accord Healthcare.

Patients will be followed prospectively for up to one year from the date of signed informed consent (enrolment) in order to ascertain patient outcomes for this time period. Follow-up will end with withdrawal of consent, loss to follow-up, death, or end of study data collection, whichever comes first.

Figure 1. Study schema and variables/data of interest

| Enrolment | | 12-month study period | | End of Study |
|---|---|---|---|---|
| Eligibility<br>Informed Consent | | Data collection (aligned with standard medical practice)<br>Relugolix treatment<br>Other prostate cancer treatment<br>Disease evolution<br>All AEs, related and not related | | Vital status<br>Disease evolution<br>Relugolix treatment<br>Other prostate cancer treatment |
| Data collection:<br>Demographics<br>Baseline clinical characteristics<br>Prostate cancer history<br>Relugolix treatment | | | | |

**End of Study**

The end of study is considered as the date of last scheduled data collection as shown in the schedule of assessments or withdrawal of the last patient. The final data from the study site will be sent to the sponsor after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

## 8.4. Schedule of Assessments

| Assessment | Enrolment | Data Collection* | End of study |
|---|---|---|---|
| Confirmation of eligibility | X | | |
| Signed informed consent | X | | |
| Demographic and baseline clinical characteristics | X | | |
| Prostate cancer history | X | | |
| Relugolix treatment | X | X | X |
| Other prostate cancer medication | X | X | X |
| Prostate cancer evolution | | X | X |
| AEs | | X | X |
| End of study | | | X |

* data collection will occur a minimum of every six months.

## 8.5. Loss to Follow-up

Participating sites will be requested to extract data from the medical record and enter it into the EDC at inclusion, at a minimum of every 6 months and at the end of the study.

A patient will not be considered lost to follow-up unless the site has not been in contact with the patient for 12 months or longer. Lost to follow-up is defined as a patient for whom no new data have been received or logged into source documents by the participating site for over twelve months and attempts to contact the patient and/or secondary contacts by phone calls and letter have been unsuccessful and exhausted.

## 8.6. Variables

Case report forms (CRFs) will be specifically designed for the collection of data from this study. An overview of the categories of study variables (raw data) to be collected for each enrolled patient is summarized in Table 2.

**Table 2 – Study assessments and data/variables of interest**

| **Category** | **Assessments / data/variables of interest** |
|---|---|
| **Confirmation of eligibility** | Eligibility assessment |
| **Demographics /Baseline clinical characteristics** | Country<br>Age<br>Ethnicity<br>Height<br>Body weight<br>ECOG PS<br>Baseline disease stage<br>Location of metastases<br>Baseline PSA level<br>Baseline testosterone<br>Prior prostatectomy<br>Prior radiotherapy<br>Prior other local intervention<br>Prior ADT<br>Most recent ADT (name, dose, last injection date)<br>Concomitant medications for PCa<br>CV Comorbidities / CV risks |
| **Medical History** | PCa date of diagnosis<br>cTNM at diagnosis<br>Gleason total score at diagnosis<br>PSA at diagnosis<br>Disease state at diagnosis |
| **Relugolix** | |
| Initiation Section | Date of treatment initiation<br>Reason for initiation<br>Loading dose<br>Daily dose<br>Switch from another ADT<br>Which ADT |
| Continuation Section | Daily dose<br>Treatment interruptions during observation period<br>Duration of the interruption<br>Reason for the interruption |
| Discontinuation Section | Date of discontinuation<br>Reason for the discontinuation |

**Table 2 (continued) – Study assessments and data/variables of interest.**

| Category | Assessments / data/variables of interest |
|---|---|
| **Disease evolution** | Disease state<br>Location of metastases<br>TNM<br>PSA level<br>Testosterone checked<br>_date<br>_Testosterone level<br>Prostatectomy<br>Radiotherapy<br>Other local intervention |
| **Concomitant medications for prostate cancer (during the follow-up)** | Name of the drug(s)<br>Date of initiation<br>Daily dose<br>Date of discontinuation |
| **Safety** | All AEs<br>-Date of apparition<br>-Type<br>-Seriousness / Severity<br>-Causality |
| **End of study** | Status<br>Date of the status |

**Definitions :**

**Effectiveness :**
Relugolix effectiveness will be assessed through serum testosterone levels obtained during the course of the study, measured at least one week after treatment initiation.
An effective castrate level is defined as a level of testosterone < 50 ng/dL (1.7 nmol/L), and a profound castrate level as a level of testosterone < 20 ng/dL.
Serum testosterone levels obtained after discontinuation will not be used to assess the effectiveness. as an exploratory parameter. Testosterone recovery is defined as a testosterone above baseline level or 280 ng/dL.

**Persistence:**

Treatment persistence is the period between treatment initiation and treatment discontinuation.

Treatment duration in weeks = (the date of last dose – the date of first dose + 1) / 7

**Adherence:**

Treatment adherence will be determined based on the information reported by the patients to the investigator.

Adherence will be documented as follows:

- No interruption during the last observation period.
- Interruption during the last observation period of:
  - Less than or equal to 7 consecutive days
  - 8-14 consecutive days
  - 15 or more consecutive days

## 8.7. Data Sources

Data will be extracted from the patient's medical records by site personnel. Once written informed consent has been obtained, study site personnel will complete the data collection at enrolment and throughout the study period for each patient. Follow-up data for patient visits will be recorded in the patient chart in accordance with the clinical site's standard of care or clinical judgment.

No mandatory visits, tests, or clinical assessments are required for this study.

All available data will be entered into eCRFs at the time of collection , at a minimum of every six months, and at the end of the study, by the site.

All AEs will be entered into the eCRF upon notification by the patient (e.g., reported via phone call) or upon identification from electronic medical record review. All serious AEs (SAEs) will be reported to the sponsor within one business day of the investigator/site being made aware using a Safety Report Form.

## 8.8. Study size

The study will enrol approximately 300 patients diagnosed with prostate cancer treated with relugolix, regardless of other prostate cancer therapies received before or at enrolment.

## 8.9. Data management

PI-delegated staff will populate the content of patients' CRFs, and all the clinical data will be recorded into EDC. Any additional information that needs recording but is not relevant for the CRF (such as signed consent forms etc.) will be recorded on a separate paper source document. The study database will be maintained by the CRO on a secure server located in European zone in accordance with written security policies. The EDC system must meet approved established standards for the security of health information and be validated. The system is developed in accordance with a rigorous system development life cycle and quality program, which ensures compliance with regulatory agency guidelines.

Data will be backed up at intervals (daily, weekly, and monthly retained for one month, three months, and six months, respectively) that comply with the CRO's standard operating procedures and details on frequency of back-ups will be provided in a study specific Data Management Plan. Patient confidentiality will be strictly maintained. Patient identifying information will be collected for the purposes of tokenization using software that separates Personal Identifiable Information in a secure location to be used only for the purposes of assigning a unique ID (the token). This process facilitates privacy compliant identification of identical patients across different data sources such as insurance and pharmacy claims data and medical records for encounters that occur outside of the investigator's office. All reported data from sites participating in the study will be entered into a secure web-based EDC study database. Site personnel will be provided with secure usernames and passwords in order to enter study data into the EDC system. All sites will be fully trained in using the EDC system, including eCRF completion guidelines. All participating sites will only have access to view and enter the data for their own patients. The CRO will maintain high data quality standards and utilize processes and procedures to repeatedly ensure that the data are as clean and as accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect and prevent the entry of out-of-range or anomalous data, as well as programmed reports and listings where programmed data quality checks are not possible (e.g., text fields). The eCRF will include options to indicate when data are not available; otherwise, key missing variables will be identified through programmed data checks and will be queried. All AE data will be coded by body system using the MedDRA and concomitant medications will be coded by drug class using the World Health Organization Drug dictionary (WHO-Drug).

The Trial Master File (TMF) will be maintained by the CRO and will be held at the CRO for the duration of the trial. The completed TMF will be transferred to the Sponsor at the end of the study for long term archiving.

## 8.10. Data Analysis

The primary goal of this study is to establish a database of clinical data from patients with prostate cancer treated with relugolix in a real-world practice setting that will characterize treatment patterns for prostate cancer and associated effectiveness and treatment persistence.

As such, no formal hypotheses will be tested in this study.

Demographic and medical history will be summarized using descriptive statistics (i.e., number and percent for categorical variables, and n, mean, standard deviation (SD), standard error (SE) of the mean, median, minimum, and maximum for continuous variables).

Treatment patterns and dosage changes will also be summarized using descriptive statistics.

When statistical testing is appropriate, continuous variables will be compared using Student's t test, Mann–Whitney U test, Wilcoxon, ANOVA, or Kruskal-Wallis tests, as appropriate for the variable distribution and number of groups under consideration. Similarly, categorical variables will be compared using chi-square or Fisher's exact tests.

For time to event analyses, Kaplan-Meier method will be used for generating estimates. The median survival time and 95% confidence intervals will be provided (if exists). Log rank test or Cox regression model may be used to evaluate the difference between subgroups adjusting with or without other covariates.

The frequency and percentage of patients experiencing AEs will be summarized by system organ class and preferred Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Missing data will be addressed using methods appropriate to the missing pattern (i.e., missing completely at random, missing at random and informative missingness). Details on data handling will also be included in the SAP. All reasonable attempts to obtain information related to the outcomes will be made.

Complete analytical specifications, including tables and listings, will be included in the SAP, which will be prepared separately. All analyses will be performed in the safety set defined as all patients who received any dose of relugolix.

## 8.11. Quality Control

Accord Healthcare has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and applicable regulatory guidelines. As such, in order to fulfil these obligations and to maintain current knowledge of the study progress, The Sponsor MSLs will regularly contact the study sites either by telephone, email or in-person visits. Regular inspection of the study data may be conducted to assess patient enrolment, compliance with protocol procedures, and completeness and accuracy of data entered on the study. Verification of eCRF data against original source documents, and occurrence of AEs may be done at selected sites and/or for selected patients.

### 8.11.1. Monitoring

Due to the non-interventional nature of this study – no routine site monitoring is planned. The site must complete the eCRFs in a timely manner and on an ongoing basis (at a minimum of every 6 months for each enrolled patient) to allow review per the Monitoring Plan:

- To improve and secure data quality, automatic data checks upon data entry will be done within the eCRF. In the eCRF, plausible ranges of values for numeric data entries as well as logical data entries and listings will be provided for each entry field. Based on this, checks on completeness and plausibility will be performed upon data entry in the eCRF. Validity of data entry thus is ensured by integrated validation checks performed by the system, indicating missing or implausible entries to the document list or investigator. All corrections will be visible from the systems audit trail.

- To ensure data collection remains current for their enrolled patients, the MSL of the Sponsor plan to conduct regular calls with the site.

- Data collection for each patient is at baseline, at a minimum of every 6 months, and end of study. Sites will be encouraged to enter data as soon as possible following these data collection points but at least within 1 month.

- If there have been no data entered by the site for an enrolled patient within 7 months of the last data entry time point, the MSL of the Sponsor will contact the site to confirm the patient's status and whether the patient is still under the Healthcare Provider's (HCP) care.
- If the patient is still participating in the study, the MSL will remind the site that data must be entered at least within six months for each enrolled patient and will confirm with the site when the data will be entered.

### 8.11.2. Auditing Procedures

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are fulfilled. Accord Healthcare or its representative may conduct audits at the clinical sites including, but not limited to, presence of required documents, the informed consent process, and comparison of CRFs with source documents. All medical records (progress notes) must be available for audit. The site agrees to participate with audits conducted at a convenient time in a reasonable manner.

### 8.11.3. Source Document Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, and recorded data from automated instruments. All source documents from this study will be maintained by the site and made available for inspection by authorized persons. The original signed informed consent form (ICF) for each patient shall be filed with records kept by the site and a copy shall be given to the patient.

### 8.11.4. Record Maintenance

Records will be retained in accordance with the applicable local regulations. All essential study documents, including records of patients, source documents, signed ICFs, and eCRFs, must be kept by the investigator for at least 15 years from study termination/completion or until instructed in writing by Accord Healthcare that records may be destroyed or forwarded to Accord Healthcare. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to audit by Accord Healthcare and its representatives. If an investigator moves, withdraws from the study, or retires, the responsibility for maintaining the records must be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by Accord Healthcare.

## 8.12. Limitations of the research methods

NIS are appropriate and relevant means for obtaining information about the use of medicines in everyday therapeutic practice and thus for investigating prospectively questions in everyday therapeutic practice.

Selection bias could occur at the site level and the patient level. Consecutive enrolment will be employed to minimize selection bias. To minimize site level bias, multiple investigators will be recruited in each country from a diverse geographical spread.

Information bias will be minimized by the use of standard eCRF, and physicians' training on the study protocol.

This study is descriptive and is not designed to assess a specific hypothesis.

The results of a non-interventional study are dependent on the correct completion of the study materials and the availability of a detailed, complete patient records. We have outlined a number of quality control steps to be taken as part of the study procedures to minimize the impact of this limitation.

# 9. Protection of Human Patients

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant Accord Healthcare Standard Operating Procedures (SOPs), and applicable privacy laws, and local regulations for each participating site.

Standard medical care remains in the responsibility of the treating physician of the patient. The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

## 9.1. Study approval, patient information and informed consent

Prior to the collection of any study related data, IRB/IEC and the Competent Authorities approval of the protocol, informed consent, and all patient enrolment materials will be obtained for each site.

Prior to any data collection under this protocol, a written ICF and a privacy statement must be signed by the patient in accordance with local practice and regulations. Information about the study will be explained to the patient where appropriate. A copy of the ICF, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent must be documented in the patient's medical records prior to any data collection under this protocol. The ICF must not be altered without the prior agreement of the relevant institutional review board (IRB) and Accord Healthcare.

## 9.2. Data protection and confidentiality

All information obtained during the conduct of the study with respect to the patient's state of health will be regarded as confidential.
Sites must ensure that each patient's anonymity is maintained. Patients must not be identified by name on the eCRF, and other documents submitted to the study.
Documents that are not for submission to the study (e.g., ICF), will be maintained by the site in strict confidence, except to the extent necessary to allow monitoring by Accord Healthcare or its representative, and auditing by Accord Healthcare. No documents identifying patients by name will leave the clinical site and patient identity will remain confidential in all publications related to the study.

Patient confidentiality is a fundamental principle of the study and will be maintained at all times. The Sponsor will ensure that the study is compliant with the requirements of the General Data Protection Regulations (GDPR) and Data Protection Act 2018. All investigators and study site staff must comply with the requirements of the GDPR and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

No patient identifiable data will be transferred to the sponsor, CRO or data management vendor (based in the UK). All patients will consent for their anonymised data to be transferred and stored on secure servers and/or on the data management vendor's (OXUS Technologies Limited) premises within the UK. OXUS Technologies will not share patients' data with third parties or transfer their data outside Europe under any circumstances.
Patients will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with local legislative requirements.

# 10. Management and Reporting of Adverse Events

AEs will be collected from the time of first dose on relugolix until the last contact, including electronic, with the patient. Accord Healthcare or its designee will follow all applicable regulatory requirements related to AE reporting.

Study investigators must also comply with the applicable regulatory requirements for reporting of serious events to the IRB responsible for reviewing information from the study at their site.

Once the investigator/site becomes aware of a reportable event, all serious AEs should be reported on a Safety Report Form. Serious AEs should be reported no later than within 1 business day of the site becoming aware of the event, along with an assessment of severity and causality.

The investigator/site will also submit any updated serious AE data to the sponsor within one business day of it being available. AEs will be captured in EDC.

The investigator is not obligated to actively seek adverse events information after conclusion of individual patient study participation. All Serious AEs should be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up. Accord Healthcare will receive and process these reports for regulatory reporting as appropriate.

## 10.1. Definitions

**AE:** Any untoward medical occurrence in a patient administered a pharmaceutical product or device and that does not necessarily have a causal relationship between the product and the event. An AE can, therefore, be any unfavourable or unintended sign (including an abnormal laboratory finding) or symptom temporally associated with a medicinal product, whether or not related to the medicinal product.

**ADR:** A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product (relugolix) and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

**Serious ADR:** An adverse reaction which:

• Results in death

• Is life-threatening

• Requires inpatient hospitalization or prolongs hospitalization

• Results in persistent or permanent disability or incapacitation

• Results in a congenital anomaly or birth defect (in a partner pregnancy)

Any important medical reaction that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient, or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above, should also be reported as a Serious AE. Serious AEs must be reported, as described below, within 1 business day of awareness of the investigator/site.

**Causality Assessment (relationship to relugolix):** The investigator is obligated to assess the relationship between relugolix treatment and the occurrence of each serious adverse events or nonserious adverse event that leads to the discontinuation of relugolix based on clinical judgement. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. The investigator should also consult the relugolix Product Information in his/her assessment.

For each serious adverse event and nonserious adverse event that leads to the discontinuation of relugolix, the investigator must document in the medical notes that he/she has reviewed the event and has provided an assessment of causality.

There may be situations in which a Serious AE has occurred, and the physician has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event.

The investigator may change his/her opinion of causality in light of follow-up information and send a Safety Report Form follow-up report with the updated causality assessment.

The following definitions are to be used when reporting the relationship of the Serious AE.

• **Definitely related**: A clinical event or laboratory test abnormality, with plausible relationship to drug intake and cannot be explained by disease or other drugs, the response to withdrawal plausible (pharmacologically, pathologically) and the event is definitive pharmacologically or phenomenologically, with satisfactory rechallenge if necessary.

• **Probably related:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (de-challenge).

• **Possibly related:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

• **Not related:** A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

• **Unclassifiable:** Report suggesting and adverse reaction but cannot be judged because information is insufficient or contradictory and that data cannot be supplemented or verified.

**Severity:** The investigator will make an assessment of intensity for each serious AE reported during the study according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).

For terms not specified with the CTCAE, the criteria below should be used to determine the grade severity:

• Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

• Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

• Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

• Grade 4 Life-threatening consequences; urgent intervention indicated.

• Grade 5 Death related to AE.

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

**Note**: An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe. If the event is an SAE, then all applicable seriousness criteria must be indicated as listed above.

## 10.2. Serious Adverse Events

The investigator is responsible for reporting all Serious AEs on a Safety Report form (by fax or e-mail to the contact information on the form). Serious AEs should be reported to the sponsor no later than within 1 business day of the investigator/site becoming aware of the event, along with an assessment of severity and causality.

# 11. Plans for Dissemination and Communication of Study Results

At the end of the study a full report will be prepared within six months of study completion that will include a narrative of the conduct and results of the study, and a statistical report including a description of the analysis performed and other documentation as may be appropriate.

Accord Healthcare may prepare one or more abstracts or manuscripts for publication including a description of the study methods and one or more abstracts or manuscripts describing the results of this observational study. Any manuscripts will be submitted to a peer-reviewed journal or submitted as abstracts/presentations at medical congresses under the oversight of Accord Healthcare.

Accord Healthcare is committed to adhering to the prevailing standards for "Good Publication Practice". Current guidelines and recommendation will be followed (e.g., GPP3 Guidelines, STROBE), as well as the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE, 2010, von Elm, 2008, Battisti, 2015).

These criteria will be applied in consideration of involving the study investigators on publications.

The results of the study including all obtained data will be the property of the Sponsor. However, the Investigator and CRO may seek permission to publish results of the study from the Sponsor. On approval from sponsor, the investigator may publish the data. For any publication related to this study, the publication policy of Sponsor, Accord Healthcare, will be followed. Unpublished data cannot be disclosed to any third party by the Investigators without written approval of the Sponsor.

No individual investigator may publish on the results of this study, or their own enrollees, without prior approval from Accord Healthcare.

# 12. References

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4. Orgovyx. European Medicines Agency Assessment Report. February 2022
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6. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects [Internet]. 2018 [cited 2019 Dec 10];Available from: https://pdf-it.dev.acw.website/please-and-thank-you?url=https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/&pdfName=wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects
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# Annex 1: Investigator Agreement

**Protocol Title:** RENAISSANCE - A multi-centre, non-interventional study of RElugolix as aNdrogen-deprivAtion therapy In patientS with advanced hormone-Sensitive prostate cANCEr.

**Protocol Number:** ACC-RNI-001

I, the undersigned, have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated. I agree to conduct the study in accordance with this protocol and to comply with all requirements regarding the obligations of investigators and all other pertinent requirements of ICH E6 (R2) Guideline on Good Clinical Practice; Declaration of Helsinki (Fortaleza, 2013); as per any other applicable regulatory requirements.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

**Principal (Site) Investigator:**

Name and academic degree: Give only academic degree _____

Function / Title: _____

Institution and Address: _____

_____

_____

Telephone Number: Give country code _____

Email address: _____

Signature: _____ Date: (DD MMM-YYYY) _____

**Notes:**

- If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor or its designee.
- Please retain original page of the Investigator's declaration at the site and send a copy of this page to the CRO.

**----------LAST PAGE----------**

# Relugolix NIS protocol 19022024

Final Audit Report 2024-03-05

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