Investigator-Sponsored

Trial Program

ardelyx®

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Contents

As part of the Ardelyx commitment to the medical and patient community, we support independent research that aligns with our values and mission to improve our scientific and clinical understanding of tenapanor and disease areas of interest.

With integrity and dedication, we make a difference by enhancing the practice of medicine and ultimately improving patient care.

Introduction

Ardelyx is dedicated to improving the lives of patients by discovering and developing first-in-class targeted therapies that advance patient care. To this end, Ardelyx supports independent research studies aligned with our mission and values from customers, third-party researchers, or collaborative groups of scientists, so-called Investigator-Sponsored Trials (ISTs).

An IST is a clinical trial that is initiated, developed, designed, and managed by a qualified Investigator who assumes sole and full responsibility for conduct and management of the study. ISTs are intended to answer an unmet scientific question or developmental need. Together with Ardelyx-sponsored research, these independent studies support the body of knowledge around disease areas of interest and real-world experiences with Ardelyx therapies.

The Investigator may request funding, support, and/or study drug, but the IST is independent and free of any inappropriate Ardelyx influence or participation. As the sponsor of the study, the Investigator retains full responsibility and control of the design, initiation, management, data analysis, monitoring, and reporting.

The following information provides a description of the requirements that must be fulfilled before support will be considered by Ardelyx and highlights your obligations as the study sponsor when your IST is being supported by Ardelyx.

Ardelyx Areas of Interest

Mechanism of Disease

Examining proposed and/or novel mechanisms of irritable bowel syndrome with constipation (IBS-C) or hyperphosphatemia (HP) pathophysiology

Tenapanor Mechanism of Action (MOA)

Understanding the role of sodium/hydrogen exchanger isoform 3 (NHE3) in intestinal biology

Exploring the effect of tenapanor on visceral hypersensitivity, the intestinal microbiome, motility, intestinal permeability, tight junction proteins, and transepithelial electrical resistance (TEER)

Management of IBS-C or HP

Understanding the burden of IBS-C or HP, and current management options for patients

Increasing awareness about unmet needs in IBS-C or HP patient populations

Clinical Outcomes of Disease Management Strategies

Review of evidence of safety and efficacy of tenapanor in patient populations

Novel Uses for Tenapanor

Advances in the understanding of the role of NHE3 in human health

Requirements (Feasibility) to Conduct a Clinical Study

All IST Investigators must be independent of Ardelyx, qualified to conduct the intended research, comply with all legal and regulatory responsibilities of the IST, and adhere to all the requirements of a study sponsor.

Ardelyx will not support requests from organizations that discriminate on the basis of age, political affiliation, race, national origin, ethnicity, gender, disability, sexual orientation, or religious beliefs.

IST requests must be unsolicited, must not provide nor promise benefits to Ardelyx, and their eligibility for review must not be influenced by Ardelyx employees.

Should you have any questions on these requirements, please email IST@ardelyx.com.

To submit an IST concept, submit an IST concept form at https://ist.ardelyx.com/submit.

Investigator Qualifications

The following documents must be provided:

- A curriculum vitae (CV) or resume which documents previous clinical research experience of the proposed IST Investigator(s) and other key research staff
- Evidence of good medical standing, including no restrictions by a regulatory authority (debarment) to undertake clinical research

Minimum Application Criteria

Potential IST Investigators must submit an application that includes, at a minimum:

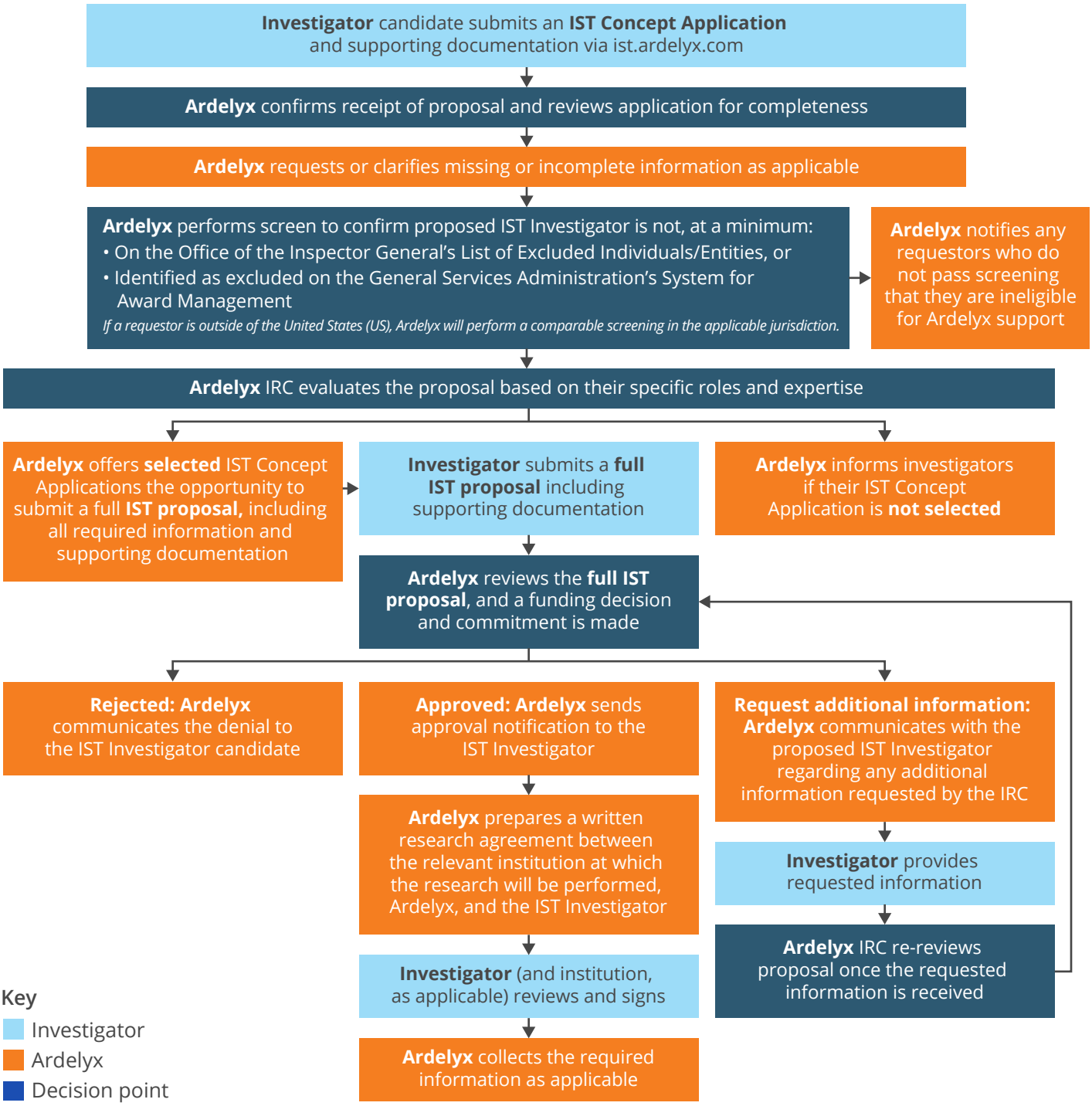
- A detailed description of the proposed IST protocol, including the nature and scope of the support requested, proposed research objectives, methodology, and top-line funding request
- Detailed study budget, including, when requested by Ardelyx, itemization of costs and services
- Proposed IST timelines and milestones, including a description of anticipated post-IST activities and/or publications
- Any additional relevant supporting documentation required by the IST Review Committee (IRC)
- Transparent responses related to funding and other third-party obligations associated with this study or the relationship with Ardelyx

The Investigator must have the appropriate infrastructure in place and capability to conduct the study proposed.

Overview of the Submission/Application Process

We welcome unsolicited proposals from qualified Investigators with novel and promising study ideas aligned with Ardelyx areas of interest.

IST proposals are reviewed in 2 phases in a formalized, centralized review and decision-making process. Submissions are reviewed on a monthly basis.



Although we appreciate each application we receive, Ardelyx cannot support every application for funding.

IST Policies

In considering an IST concept and proposal, the following will be considered:

1. Overall scientific merit and value to the scientific community (eg, research that investigates a previously unanswered question)
2. Proposed IST Investigator independence in the development and submission of the proposal, which should be free of any inappropriate Ardelyx influence or participation
3. Consistency with Ardelyx's scientific and research objectives
4. Consistency with Ardelyx's strategic objectives for a particular product, if the requested IST support includes provision of Ardelyx product for performance of the IST
5. Whether the risk/benefit profile for potential patient(s)/subject(s) is appropriate and acceptable
6. Whether any undue risk or harm may be posed to patients and whether the protocol meets ethical guidelines concerning human subjects in research and/or applicable animal welfare guidelines
7. Any past incidence of proposed IST Investigator compliance problems, such as debarment or disqualification by the US Food and Drug Administration (FDA)
8. Qualifications and expertise of the Investigator(s) and, where applicable, subinvestigator(s), including the Investigator's ability to complete the study or project as proposed
9. Consistency of proposed costs with planned research activities and whether they represent fair market value (FMV)
10. Funding amounts must be reasonable for the activities proposed and funds must only be used for the expenses described in the proposal and the IST agreement
11. The availability of funding, support, and/or study drug requested

Overview of the IST Process

Receipt of Funding/Study Drug

The purpose of IST funds is only to further the scientific research and knowledge within a particular therapeutic area. IST funds cannot be provided to gain experience with a study drug or treatment protocol.

Following the initiation of a study, funding will be released as key milestones are achieved, in accordance with the payment schedule noted in the IST Agreement.

Please note that all other payment milestones will depend on the study design and the schedule noted in the IST Agreement and could include milestones based on recruitment.

Funding for the IST must be based on FMV of the activities contemplated in the protocol and payments may not be tied to whether the study results reflect favorably or unfavorably on the company product being studied.

IST support may not be awarded with the intent to develop or retain customer relationships, to provide exposure to Ardelyx products, or to induce or reward the recommendation, prescription, use, purchase, or referral of Ardelyx products.

Furthermore, IST funds may not be used to pay for the Investigator's ordinary operating expenses not related to the IST (ie, expenses of activities that the recipient is already required to perform or customarily performs) or support research that has already occurred.

Ardelyx may not conduct any return on investment (ROI) analyses or assessments of the effects of the IST participation on the IST Investigators' prescribing practices or the effect on product sales.

Upon completion of the IST, a financial reconciliation must be made by the IST Investigator and any unused funding, in-kind support, or product provided must be returned to Ardelyx.

The following items must be in place and provided to Ardelyx prior to release of study drug and/or funding:

Finalized budget and fully executed contract

Documentation of institutional review board (IRB)/ethics committee (EC) approval

Collaboration with Ardelyx and documentation of investigational new drug application (IND)/clinical trial application (CTA) approval, as applicable

Active pharmacy license if product is requested

Completed W-9 form

Conducting the IST

Study Status, Reporting, and Registry in a Public Database

In accordance with the Ardelyx IST Agreement:

1. Ardelyx will receive regular updates and/or summaries for each IST within a reasonable timeframe

2. Any changes in support or modifications of protocol must be reviewed by Ardelyx and memorialized in an amendment to the IST Agreement

3. Results of the IST must be reported as applicable to ClinicalTrials.gov and/or any other relevant health authority (HA) pursuant to applicable laws and regulations

4. An IST Investigator who authors any publication, abstract, or poster presentation must disclose Ardelyx support of the research per the requirements of the relevant journal or conference, as well as local laws, regulations, and standards for venues outside of the US

5. IST Investigators should provide enrollment data, confirming that safety information is being shared with Ardelyx as required

Safety Reporting Requirements

One of the most important requirements of an IST Investigator is the responsibility to monitor and report safety data to the appropriate authorities in a timely and accurate manner.

In addition to reporting safety data to all relevant authorities, you will have the responsibility to report the safety information to Ardelyx in accordance with the IST Agreement.

The IST Investigator has primary responsibility to report adverse events (AEs) attributable to any Ardelyx product to regulatory authorities and must also provide to Ardelyx any information about drug-related deaths, serious AEs, other significant information regarding the safety of a Ardelyx product, and/or additional safety-related information, as specified in the agreement.

The timelines for providing this information to Ardelyx will be specified in the IST Agreement.

Ardelyx will provide the IST Investigator with appropriate materials to meet current safety reporting requirements prior to the initiation of research, as requested in writing. Ardelyx will notify the IST Investigator of relevant safety data throughout the duration of the project as new or updated safety information becomes available.

Study Results and Publications

Ardelyx encourages IST Investigators to publish the results of ISTs. Ardelyx will not be involved in authorship selection or writing and will not be listed as a coauthor. The IST Investigator shall publish data in accordance with the publication plan set forth in the IST application and shall control his or her publication or presentation in a manner that underscores his or her independence from Ardelyx.

Ardelyx shall receive copies of unpublished manuscripts or abstracts in order to review them in advance of submission for publication or for a scientific meeting presentation. Ardelyx review and commentary should be limited to correcting or revising errors pertaining to Ardelyx products or to address confidentiality or intellectual property concerns.

The IST Investigator retains the right to reject or accept Ardelyx's comments at his or her discretion, with the exception of requested changes to prevent disclosure of Ardelyx's confidential or proprietary information, which must be accepted.

An IST Investigator who authors any publication, abstract, or poster presentation must disclose Ardelyx support of the research per the requirements of the relevant journal or conference, as well as local laws, regulations, and standards for venues outside of the US. Authorship should reflect the role actually provided by the individual in the conduct of the underlying research consistent with the Policy on Publication of Research Data.

Overview of Key Responsibilities of Ardelyx and the Investigator

The Investigator will:

- Develop the research proposal
- Provide information to Ardelyx as requested
- Submit the IRB/IEC file at the start of the study and for annual renewals
- Submit protocol amendments to the IRB/IEC
- Ensure that the IRB/IEC-approved protocols are being adhered to in accordance with Good Clinical Practice (GCP), applicable guidelines, and local and international standards
- Register the IST in a public database, such as www.clinicaltrials.gov, after the contract is fully executed
- Implement, conduct, and monitor the clinical research and data collection
- Maintain accurate clinical records of the study and ensure the integrity of the collected data and other attributions are aligned with GCP
- Contract third-party vendors such as clinical research organizations, statisticians, insurance brokers, medical writing agency, and couriers
- Manage and oversee participating sites and contractors
- Report safety data to Ardelyx as necessary
- Reconcile AEs as required
- Report safety data to the HAs when appropriate
- Analyze the study data; prepare interim and final study reports and send them to Ardelyx
- Prepare and submit draft publications to Ardelyx prior to submission to a scientific congress or journal
- Independently publish the results of the clinical trial

Ardelyx will:

- Evaluate the research proposal
- Request additional information, if required
- Disseminate updated, approved prescribing information for tenapanor
- Review protocol amendments
- Review draft publications for submission to scientific congresses and journals

Abbreviations

AE = adverse event

CTA = clinical trial application

CV = curriculum vitae

EC = ethics committee

FDA = Food and Drug Administration

FMV = fair market value

GCP = Good Clinical Practice

HA = health authority

HP = hyperphosphatemia

IBS-C = irritable bowel syndrome with constipation

IND = investigational new drug application

IRB = institutional review board

IRC = IST Review Committee

IST = Investigator-Sponsored Trial

MOA = mechanism of action

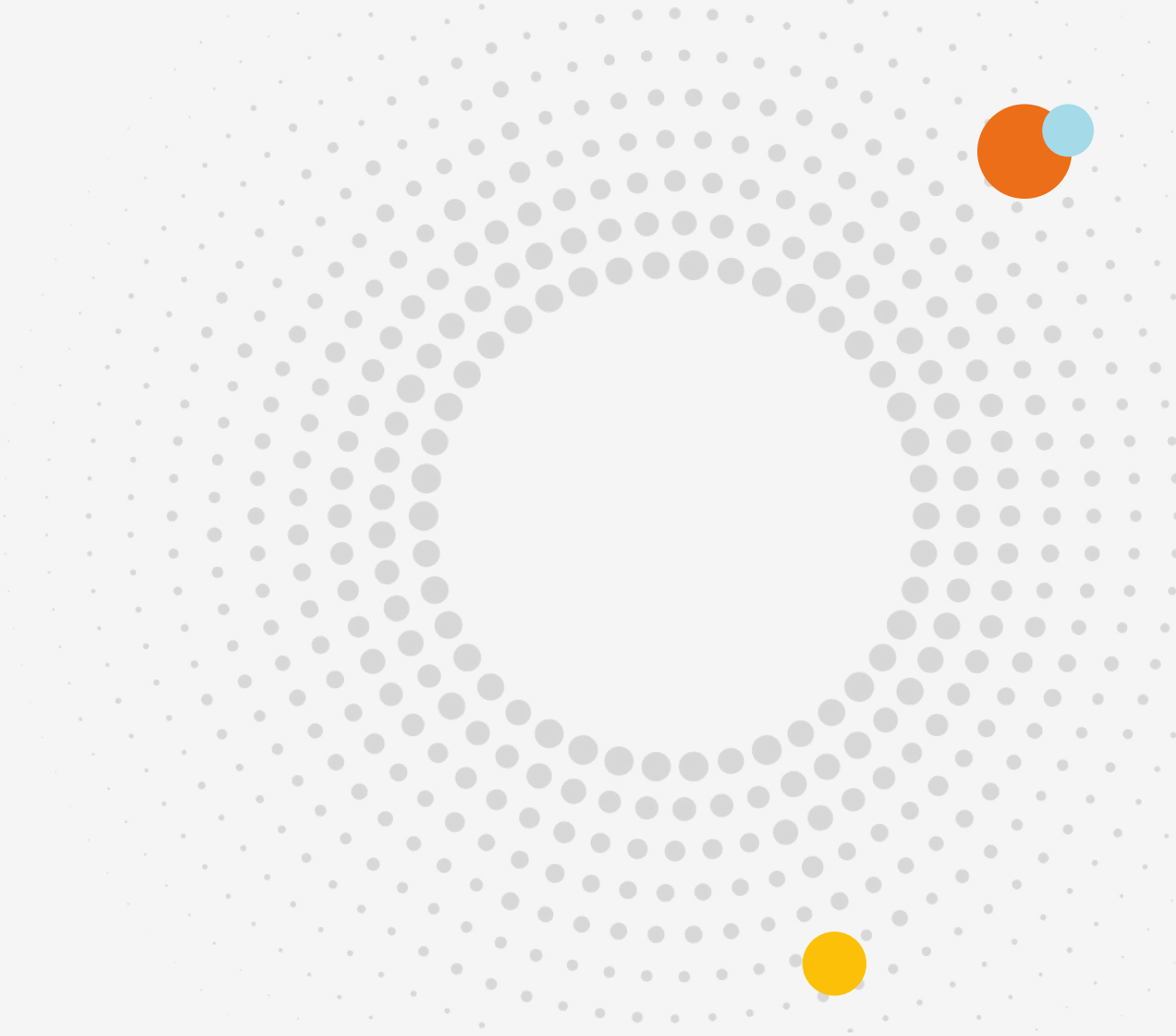
NHE3 = sodium/hydrogen exchanger isoform 3

ROI = return on investment

TEER = transepithelial electrical resistance

US = United States

If you have questions, please email ist@ardelyx.com.



In addition to the requirements set forth in this guidance document, each request will be assessed subject to applicable local laws and regulations

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