Passionately committed to improving the lives of patients by discovering, developing and commercializing first-in-class targeted therapies that advance patient care

June 2021
Forward-Looking Statements

To the extent that statements contained in this presentation are not descriptions of historical facts regarding Ardelyx, they are forward-looking statements reflecting the current beliefs and expectations of management made pursuant to the safe harbor of the Private Securities Reform Act of 1995, including statements regarding the potential for Ardelyx’s product candidates in treating the diseases and conditions for which they are being developed; Ardelyx’s expectation regarding the potential approval of its NDA for tenapanor and the expected timing thereof; Ardelyx’s expectations regarding the potential indication for tenapanor for hyperphosphatemia; the commercial potential for treating hyperphosphatemia in CKD patients on dialysis, including Ardelyx’s expectation regarding the rate of adoption and use of tenapanor, if approved; Ardelyx’s expectations regarding the size of the patient population and the size of the market for tenapanor in CKD patients on dialysis, and the potential growth thereof; and Ardelyx’s expectations regarding the exhaustion of its current capital resources. Such forward-looking statements involve substantial risks and uncertainties that could cause the development of Ardelyx’s product candidates or Ardelyx's future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the uncertainties inherent in research and the clinical development process; the uncertainties associated with the regulatory approval process; and the uncertainties in the drug commercialization process. Ardelyx undertakes no obligation to update or revise any forward-looking statements. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to Ardelyx’s business in general, please refer to Ardelyx’s Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 6, 2021, and its future current and periodic reports to be filed with the Securities and Exchange Commission.
Ardelyx Overview

• **Tenapanor: First-in-class product candidate** for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis
  – Three successful statistically significant Phase 3 studies
  – NDA Accepted September 2020
  – Extended PDUFA Date – July 29, 2021

• **Large target market**
  – ~2.7M phosphate binder prescriptions written per year in U.S.\(^1\)
  – Accessible with U.S. specialty-focused commercial organization
  – Ex-U.S. commercialization through select collaborations

• **Discovery platform** fuels additional pipeline programs
  – RDX013: novel approach for hyperkalemia
  – RDX020: novel approach for metabolic acidosis

• **Cash of $178.2M\(^2\)** supports operations into second half of 2022

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1. IQVIA 2019 (Retail); Adding estimate for Rxs through dialysis organization specialty pharmacies
2. Cash, cash equivalents and short-term investments as of March 31, 2021
Well-Established Hyperphosphatemia Market

2. IQVIA 2019 (Retail); Adding estimate for Rxs through dialysis organization specialty pharmacies
Phosphate Level is an Independent Predictor of Morbidity and Mortality in Patients on Dialysis

**Serious Potential Consequences From Elevated Phosphorus**

**Relative Risk of Death Based on Serum Phosphorus Level**

- Increased serum phosphorus levels of 0.5 to 1 mg/dL over the reference range resulted in a significant increase in relative risk of death.

Elevated serum phosphorus also increases the relative risk of hospitalization by up to 38%.

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Majority of Patients are Unable to Consistently Maintain Target Phosphorus Levels Despite Active Management with Currently Available Therapies

4.1.2. In patients with CKD G3a–G5D, we suggest lowering elevated phosphate levels toward the normal range\(^1\) (Adults: 2.5 to 4.5 mg/dL)

77% of patients treated with binders were unable to consistently maintain phosphorus levels <=5.5 mg/dL over a six-month period\(^2\)

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2. Spherix RealWorld Dynamix, Dialysis 2019
Tenapanor Clinical Development Program
Tenapanor: A First-In-Class Phosphate Absorption Inhibitor

**TARGETS**  
primary pathway of phosphate absorption

**BLOCKS**  
paracellular absorption of phosphorus

**DOSED**  
as one pill twice per day

1. Inhibits NHE3, reducing sodium absorption resulting in modest intracellular proton retention
2. Proposed induction of conformational change in claudin proteins
3. Specifically blocks absorption of phosphate through the paracellular pathway

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2. In clinical trials, dosing is 1 pill BID
Tenapanor Clinical Data Package is Robust

**BLOCK**
Phase 3 – Short Term
Primary and Secondary Endpoints met

**PHREEDOM**
Phase 3 – Long-Term
Primary and Key Secondary Endpoints met

**NORMALIZE**
PHREEDOM Extension
Initial Analysis Demonstrates Increased % of Patients Achieving Goal

**AMPLIFY**
Phase 3 – Short Term
Primary and Key Secondary Endpoints met

Extended PDUFA Date: July 29, 2021
**HYPERPHOSPHATEMIA**

**BLOCK:** Statistically Significant Pivotal Monotherapy Phase 3 Results

**DESIGN**

12-week trial to evaluate different doses of tenapanor, as well as the efficacy, safety and tolerability of tenapanor monotherapy in patients with CKD on dialysis

n=219

Primary Endpoint: Difference in change in serum phosphorus between pooled tenapanor-treated patients and placebo-treated patients in the efficacy analysis set from the end of the 8-week treatment period to the end of the 4-week randomized withdrawal period

**Efficacy**

Primary endpoint statistically significant (p<0.01) difference in least squared mean serum phosphorus change (0.82 mg/dL) between tenapanor and placebo

Secondary analyses: At the end of the 8-week open label treatment period, tenapanor-treated patients in the efficacy analysis set (n=80) achieved a mean decrease in serum phosphorus from baseline of 2.56 mg/dL

**Safety**

Well tolerated

8-week open-label treatment period:

- 39% diarrhea
- Only adverse event ≥5%
- Mostly mild to moderate
- Stool form and frequency changes, on average, remained in normal range for healthy individuals
- 8% discontinuation due to diarrhea

**HYPERPHOSPHATEMIA**

**AMPLIFY: Statistically Significant Pivotal Phase 3 Results with Tenapanor and Binders**

**DESIGN**

To evaluate tenapanor and phosphate binders (two distinct MOAs) when used in combination

n=235

Primary Endpoint: Comparison of change from baseline in serum phosphorus at week 4 between tenapanor + phosphate binder (tenapanor arm) and placebo + phosphate binder (binder arm)

**EFFICACY**

Primary endpoint statistically significant difference in reduction of serum phosphorus levels (p=0.0004) compared to binders alone at week 4

~2 times more patients achieved the serum phosphorus treatment goal of <5.5 mg/dL with tenapanor and phosphate binders vs phosphate binders alone (P≤0.0097)

Secondary analyses: Statistically significant reduction (p-values≤0.0027) in FGF23 levels

**SAFETY**

Favorable tolerability

Well tolerated: 4% of patients in tenapanor arm discontinued vs. 2% in the binder arm

- 43% diarrhea: single adverse event with a placebo-adjusted rate >3%
- Mostly mild-to-moderate
- 3% severe diarrhea
- Transient: median resolution 4 days after onset
- Resulted in treatment discontinuations in 3 out of 116 patients
PHREEDOM: Statistically Significant Pivotal Long-term Monotherapy Phase 3 Results

**DESIGN**
52-week trial to evaluate the long-term efficacy, safety and tolerability of monotherapy tenapanor in CKD patients on dialysis
n=564

Primary Endpoint: Difference in change in serum phosphorus between pooled tenapanor-treated patients and placebo-treated patients in the efficacy analysis set from the end of the 26-week treatment period to the end of the 12-week randomized withdrawal period

**EFFICACY**
Primary endpoint statistically significant (p<0.0001) difference in least squared mean serum phosphorus change (1.4 mg/dL) between tenapanor and placebo

Secondary analyses: In the 26-week open label treatment period, 77% of tenapanor patients in the intent-to-treat population (n=408) achieved a decrease in serum phosphorus, with a mean decrease of 2.0 mg/dL

**SAFETY**
Well tolerated

26-week open-label treatment period:
- 17.2% of 419 tenapanor-treated patients vs. 22.6% of 137 sevelamer treated-patients (active safety control) experienced an SAE
- Diarrhea only adverse event >5% (52%)
- Vast majority mild to moderate; 5% severe diarrhea
Tenapanor Commercialization: Disrupting and Restating the Hyperphosphatemia Market
Favorable Payor Landscape for Hyperphosphatemia Rx Therapies

62% Medicare / 38% Commercial, Medicaid, Other

Tenapanor Launch Landscape:
70% Access and Affordability Potential


Payor Mix Estimates: Spherix RealWorld Dynamix Dialysis 2019 and USRDS 2018 Medicare Breakdown
Tenapanor Product Profile is Compelling

MOA

- First-in-Class, non-binder, phosphate absorption inhibitor
- Blocks paracellular (primary pathway) phosphate absorption

Efficacy

- All trials met primary and secondary efficacy endpoints
- Reduced serum phosphorus levels in patients with CKD on dialysis

Tolerability

- Generally well-tolerated
- Diarrhea (47%) tended to be mild-to-moderate and transient

Dosing and Administration

- One small pill
- BID dosing
Nearly 3 Out of 4 Nephrologists See a High Need for New Treatments and Expect Tenapanor to Provide an Improvement Compared to Phosphate Binders

How Much of a Need for New Treatments?

- Low need: 5%
- Moderate need: 23%
- High need: 72%

How Does Tenapanor Compare to Phosphate Binders?¹

- **Dosing & administration**
  - Much Worse / Worse: 8%
  - Same: 91%
  - Better / Much Better: 1%

- **Patient adherence**
  - Much Worse / Worse: 10%
  - Same: 90%
  - Better / Much Better: 0%

- **Efficacy**
  - Much Worse / Worse: 27%
  - Same: 72%
  - Better / Much Better: 0%

- **Tolerability**
  - Much Worse / Worse: 8%
  - Same: 33%
  - Better / Much Better: 59%

¹ Physician perceptions of tenapanor relative to phosphate binders based on tenapanor product profile. There have been no head-to-head studies comparing tenapanor to phosphate binders.

Source: Ardelyx market research study conducted by Hawk Partners, December 2019.
The Majority of Nephrologists Expect to Use Tenapanor as First Line Therapy

Most Likely First Line Hyperphosphatemia Treatment for Naïve Patients

- 60% Tenapanor
- 16% Tenapanor + Phosphate Binder
- 25% Phosphate Binder

Tenapanor Anticipated Line of Therapy

- Second line after binder failure
- Added to binders
- First line, before binders

1. Ardelyx market research study conducted by Hawk Partners, December 2019 (n=205)
2. Spherix, RealTime Dynamix Bone and Mineral Metabolism, Q1 2020 (n=202)
Establish central role of novel blocking mechanism across hyperphosphatemia treatment paradigm

Drive strong nephrology demand

Optimize patient access and affordability

Leverage market shaping activities, interest in paracellular science, and growing Ardelyx reputation as leader in advancing science and patient care

TENAPANOR is a First-in-Class, Non-Binder, Phosphate Absorption Inhibitor

THAT may make consistently achieving phosphorus targets possible

BECAUSE it blocks the primary pathway of phosphate absorption

SO THAT nephrologists, dietitians and patients can start to believe that effective, consistent phosphate control may now be possible
Hyperphosphatemia Rx market is driven by nephrologists

Call universe of nephrologists highly concentrated. Sales force territories and targets aligned to optimize opportunity

Commercial force of ~100 targeted at tenapanor opportunity – nephrologists, dialysis organizations, payors

Source: IQVIA Targeting and Segmentation analysis.
The ArdelyxAssist™ Program is Designed to Optimize Access and Affordability of Tenapanor for Patients

• Targeted payor initiatives to secure access

• State of the art patient services to support benefit investigations and prior authorization requests

• Commercial co-pay program

• Patient Assistance Program with benevolent eligibility criteria
RDX013 for Hyperkalemia

Investigational, first-in-class potassium lowering secretagogue

Leverages the GI’s natural ability to secrete potassium into the lumen of the gut to reduce serum potassium levels
RDX013-101: 112 Subject, Phase 1 Safety and Proof-of-Concept Study

- Double-blind, placebo-controlled, healthy volunteers (19-75 years old)
- 112 total: 8 groups x 14 subjects/group (12 treated and 2 placebo)
- Treatment: Different doses and dosing regimens
- 12 days/ 11 nights in phase 1 study unit; standardized meals
- Endpoints
  - Safety assessment: clinical and vital signs, hematology, blood chemistries, ECG, etc.
  - Pharmacodynamics: Change from baseline in stool potassium excretion

[Diagram showing timeline with dose and collections]
RDX013: Generally Safe and Well Tolerated

- There were no treatment-related trends in terms of AEs
- The majority of TEAEs reported were mild in severity and resolved without treatment
- There were no deaths, severe TEAEs or SAEs reported during the study
- There were no treatment- or dose-related trends in the clinical laboratory evaluations, vital signs data, 12-lead ECG data, or physical examination findings during the study
**RDX013: Comparable PD Response to Potassium Binders in Healthy Subjects at a Significantly Lower Dose**

<table>
<thead>
<tr>
<th>Binder</th>
<th>K-binding capacity (human stool data)</th>
<th>Maintenance dose</th>
<th>Fecal potassium excretion (Healthy volunteers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaPSS/CaPSS</td>
<td>~0.4-0.8 mEq/g</td>
<td>~10g – 30g QD $^1$</td>
<td>~0.4-0.8 mEq/g</td>
</tr>
<tr>
<td>Veltassa</td>
<td>~1-1.5 mEq/g</td>
<td>8.4-16.8 g QD</td>
<td>~9-17 mEq/d $^2$</td>
</tr>
<tr>
<td>Lokelma</td>
<td>1.8 mEq/g</td>
<td>5-10 g QD</td>
<td>~9-18 mEq/d $^3$</td>
</tr>
<tr>
<td>RDX013</td>
<td>NA</td>
<td>RDX013 (~100 mg) BID</td>
<td>19 mEq/d $^4$</td>
</tr>
</tbody>
</table>

1. Not approved for chronic use in US, but reported studies showed these doses reduced serum [K] by 0.9-1.0 mEq/L (7d to 9Mo studies) (LePage_2016; Yu_2017)
2. Patiromer K-binding capacity appears to be non-linear, with higher capacity at low doses; at approved doses binding capacity is ~1 mEq/g (Li_2016)
3. Lokelma K-binding capacity appears linear with dose (Lokelma package insert)
4. Data from Ardelyx Phase 1b study
RDX013-201 Phase 2 Study in CKD Patients with Hyperkalemia
RDX013-201: Study Design

Objective

Part A
• To evaluate the safety and pharmacodynamics of RDX013 at different doses to identify the best dose for further evaluation in Part B of the study

Part B
• To assess the safety and efficacy of 4-week treatment with RDX013 at the optimal dose in patients with hyperkalemia

Key Inclusion Criteria
• sK value 5.1 to < 6.5 mmol/L at Screening
• Chronic kidney disease with eGFR ≥ 15 to < 60 mL/min/1.73m², most recent historical value (MDRD or CKD-EPI formula)

Key Exclusion Criteria
• Treatment with potassium-lowering drugs (e.g. Kayexalate®, Lokelma®, Veltassa®), within 7 days prior to enrollment/randomization
• Treatment with glucocorticoids
• Treatment with aldosterone receptor antagonists
RDX020 for Metabolic Acidosis

first-in-class targeted agent for treating metabolic acidosis
Metabolic acidosis is a highly prevalent comorbidity in CKD, strongly correlated with disease progression and adverse outcomes

There are no approved treatments for metabolic acidosis

- Physicians utilize large quantities of oral alkali salts (~4-10 g/day as a starting dose)
- Treatment brings high sodium load; most CKD patients have sodium-sensitive comorbidities (hypertension, CVD, HF, edema)

Ardelyx has successfully targeted intestinal bicarbonate exchange

- Ardelyx lead compounds are potent, selective and proprietary inhibitors
- RDX020 program has the potential to be a first-in-class treatment
RDX020: Lead Compound Shows Promising Pharmacodynamic Activity

Rats dosed with RDX020-A exhibited a progressive increase in blood pH over the 6-hour time period of the experiment.

A slight increase in blood bicarbonate level was noted over time in both groups.

**Ardelyx bicarbonate secretion inhibitor modulated blood pH**

Male SD rats (n=8/group)
JVC cannulated
Route: PO, single dose
Time-points: pre-dose, 2, 3, 4 and 6 h
## Reaching Ex-US Geographies Through Partners

<table>
<thead>
<tr>
<th>Country</th>
<th>Partner</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>Kyowa Kirin Co., Ltd.</td>
<td>$30M upfront payment, up to $55M and 8.5B Yen in milestones, high-teen royalties</td>
</tr>
<tr>
<td>China</td>
<td>Fosun Pharma</td>
<td>$12M upfront payment, up to $113M in milestones, mid-teen to 20% royalties</td>
</tr>
<tr>
<td>Canada</td>
<td>Knight Therapeutics, Inc.</td>
<td>Up to CAD $25M in upfront payment and milestones, tiered royalties ranging from mid-single digits to low twenties</td>
</tr>
</tbody>
</table>

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**Maintaining flexibility in Europe**
Key Financial Items

$178.2 MM

Cash and Investments as of March 31, 2021

Cash runway into second half of 2022

~ $50 MM of debt-interest only until December 2021

~ 98.7 MM shares outstanding as of March 31, 2021
Thank You