City THERAPEUTICS

# Next Generation RNAi

**Corporate Overview**

November 2026



# Forward-Looking Statements

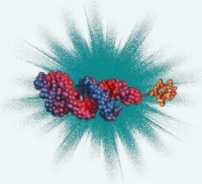
This presentation contains express or implied forward-looking statements of City Therapeutics, Inc. ("City," the "Company," "we," "us" or "our") within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. All statements other than statements of historical facts are forward-looking statements, including, without limitation, statements regarding the initiation, timing, progress, and results of the Company's research and development programs, preclinical studies and clinical trials for the Company's current or future product candidates and effectiveness of the Company's City Platform; the ability of clinical trials to demonstrate safety and efficacy of the Company's product candidates, and other positive results, and the ability of the Company's preclinical studies and earlier clinical trials to predict later clinical trial results; the timing, scope and likelihood of regulatory filings and approvals of the Company's product candidates; the implementation of the Company's business model, and strategic plans for the Company's business, programs, and current and future product candidates; the Company's ability to obtain additional cash and the sufficiency of the Company's existing cash and cash equivalents to fund its future operating expenses and capital expenditure requirements; the accuracy of the Company's estimates regarding expenses, future revenue, capital requirements and needs for additional financing; the accuracy of the Company's estimated cash runway; the size and growth potential of the markets for the Company's product candidates, and the Company's ability to serve those markets; the Company's potential and ability to successfully manufacture and supply its current and future product candidates for clinical trials and for commercial use, if approved; the Company's ability to leverage programs within its initial target indications and to progress additional programs to further develop its pipeline; the scope of protection the Company is able to establish and maintain for intellectual property rights covering its product candidates; developments relating to the Company's competitors and its industry, including competing product candidates and RNAi therapeutics; developments related to the Company's proprietary City Platform; the Company's ability to obtain funding for its operations necessary to complete further development and commercialization of its product candidates; and expectations regarding future events under collaboration and licensing agreements, including potential future payments, as well as the Company's plans and strategies for entering into further collaboration and licensing agreements. In some cases, you can identify forward-looking statements because they contain words such as "may," "will," "shall," "should," "expects," "plans," "anticipates," "could," "intends," "target," "projects," "contemplates," "believes," "estimates," "predicts," "potential," or "continue" or the negative of these words or other similar terms or expressions that concern our expectations, strategy, plans or intentions, although not all forward-looking statements are accompanied by such words. Forward-looking statements are based on assumptions and assessments made by management in light of their experience and perceptions of historical trends, current conditions, expected future developments and other factors they believe to be appropriate, and speak only as of the date of this presentation. Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or other events to be materially different from any future results, performance or other events expressed or implied by the forward-looking statements. These risks and uncertainties include, among others, those described under the caption "Risk Factors" in our final prospectus dated October 15, 2026, filed with the Securities and Exchange Commission (the "SEC") pursuant to Rule 424(b) on October 16, 2026 , and in our subsequent filings with the SEC, which are available on the SEC's website at www.sec.gov. Given these uncertainties, you should not place undue reliance on forward-looking statements. Except as required by law, we assume no obligation to update these forward-looking statements, or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future.

# Engineering the next generation of RNAi therapeutics

Founded in 2023 by RNAi pioneers who brought the first FDA-approved RNAi medicines to patients, we are applying our expertise and breakthrough science to unlock what RNAi can do next.

### Advancing a clinical pipeline across three programs

Two programs in Phase 1 across underserved patient populations, with one additional program expected to enter the clinic by year-end 2026



### A platform engineered for exceptional potency and reach

Novel trigger design, tissue-selective delivery, and genetics-led target selection combine in the City Platform – expanding RNAi beyond the liver into the eye, CNS and adipose tissues

### Led by RNAi pioneers

Our team collectively contributed to the discovery, development or commercialization of 7 of the 8 currently FDA-approved RNAi medicines

### Partnerships that validate the potential of our platform

Collaborations with Bausch + Lomb and Biogen to advance extrahepatic RNAi therapeutics for eye and CNS diseases

### Near-term potential catalysts across the pipeline and platform

Multiple clinical data readouts expected in the next two years and aiming to deliver one to two IND filings per year

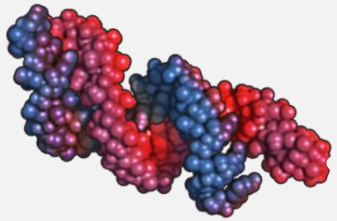
CNS: central nervous system; FDA: US Food and Drug Administration; IND: Investigational New Drug Application or equivalent

# The City Platform: The engine behind every medicine we develop

**THE CITY PLATFORM**

**CORE FOCUS**

**Enabling us to engineer high potency and specificity into every medicine we make**



- Deep RNAi therapeutics expertise
- cityRNA - proprietary, extrahepatic
- ☐AI/ML molecular design

**Novel Delivery Conjugates**

Proprietary ligands for tissue-selective delivery, including ocular, CNS and adipose cells

**Target Discovery and Selection**

Enabled by human genetics

OUR GOAL
**Optimizing siRNA to achieve best-in-class liver-directed therapeutics**

OUR GOAL
**Engineering next-generation cityRNA to expand RNAi's reach beyond the liver**

# Rapidly advancing RNAi pipeline in and beyond the liver

## Goal to file 1-2 new INDs per year across multiple tissue types

| Target Tissue | Program | Disease Area | Discovery | IND enabling | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|---|---|---|---|
| Hepatic | CITY-FXI | Thrombosis | | | | | |
| | CITY-RBP4 | Stargardt Disease | | | | | |
| | | Geographic Atrophy | | | | | |
| | CITY-TFR2 | Anemia of Chronic Disease | | | | | |
| Ocular | Undisclosed Target *Partnered with Bausch + Lomb* | Geographic Atrophy | | | | | |
| CNS | Undisclosed Target *Partnered with Biogen* | Major CNS Diseases | | | | | |

BAUSCH + LOMB

Biogen

IND: Investigational New Drug Application or equivalent

CITY-FXI

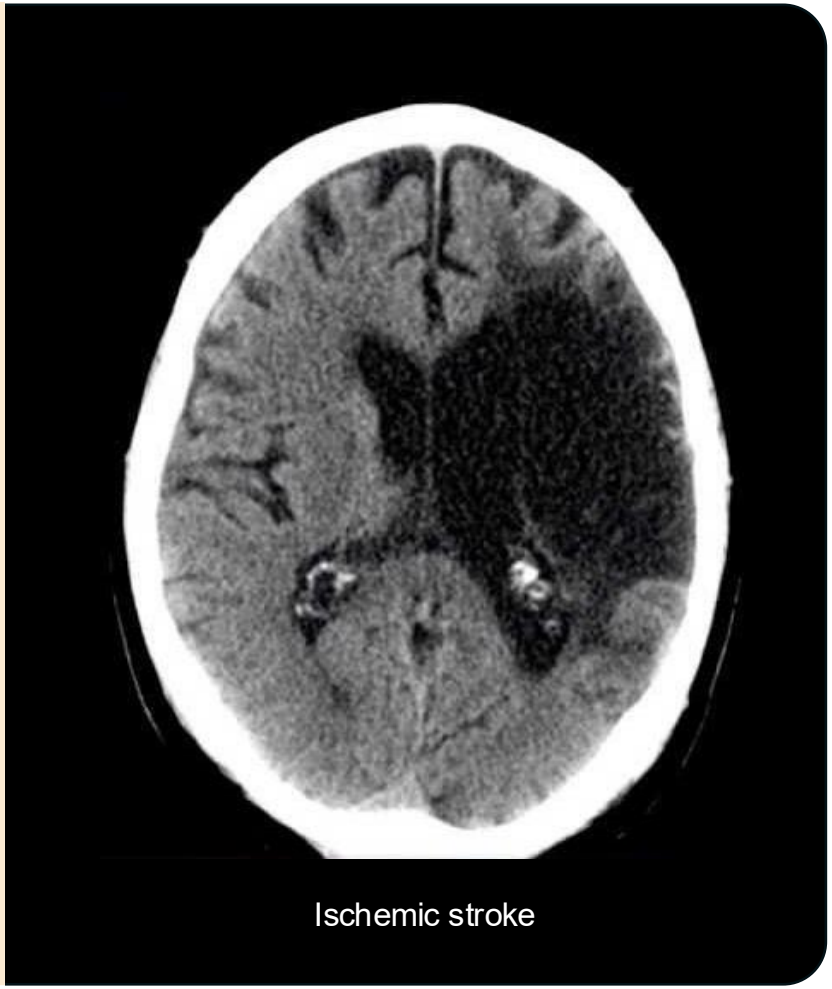
# RNAi designed to provide safe, effective, durable antithrombotic therapy

# Thromboembolic disease is among leading causes of death

**Current options remain limited by bleeding risk and adherence challenges, leading to critical gaps in care**

**Affects ~40 to 50 million globally**

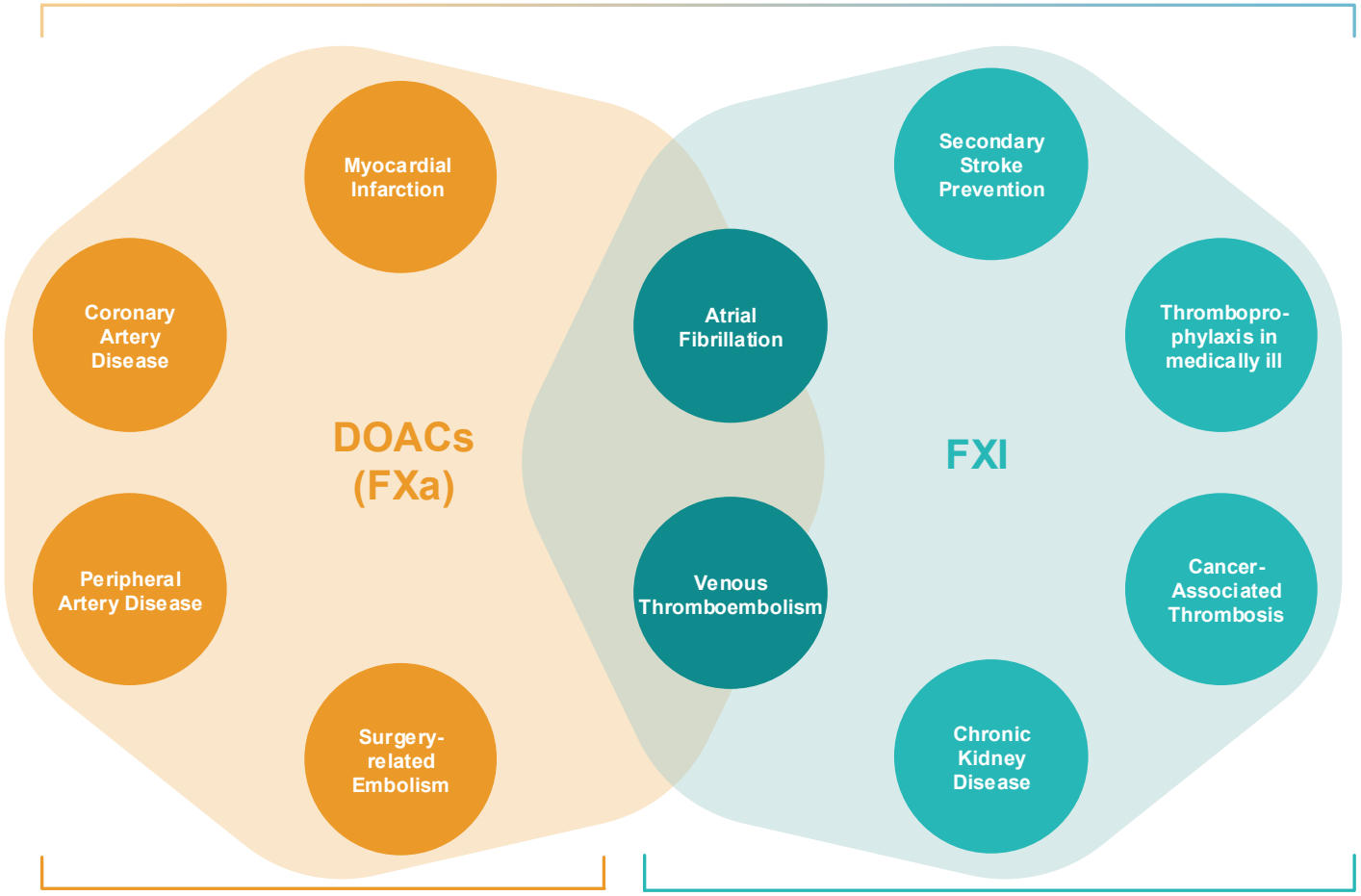
- Responsible for ~1 in 4 deaths worldwide
- Direct oral anticoagulant (DOACs) are standard of care but come with bleeding risk
- Many patients remain untreated due to bleeding risk
  - ~795,000 ischemic strokes annually in US; anticoagulation could help prevent secondary strokes, but DOACs are contraindicated
  - ~1 in 3 AFib patients with elevated stroke risk not on DOACs
  - ~250,000–350,000 VTE patients in US remain untreated or under-treated despite persistent risk factors
  - Cancer patients face 4–6x elevated VTE risk but high bleeding risk



Ischemic stroke

# FXI knockdown potentially well-suited for multiple indications

**Estimated 40-50 million patients across potential indications**




Global anticoagulants market projected to reach roughly **$56 billion by 2033**

**FXI inhibitors potentially well-suited in indications where direct DOACs are suboptimal**

**Initial focus areas[1]**

**DOAC-ineligible AFib**
~3.2 million[2]

**Secondary Stroke Prevention**
~795,000[2]

**Secondary VTE Prophylaxis**
~250,000-350,000[3]

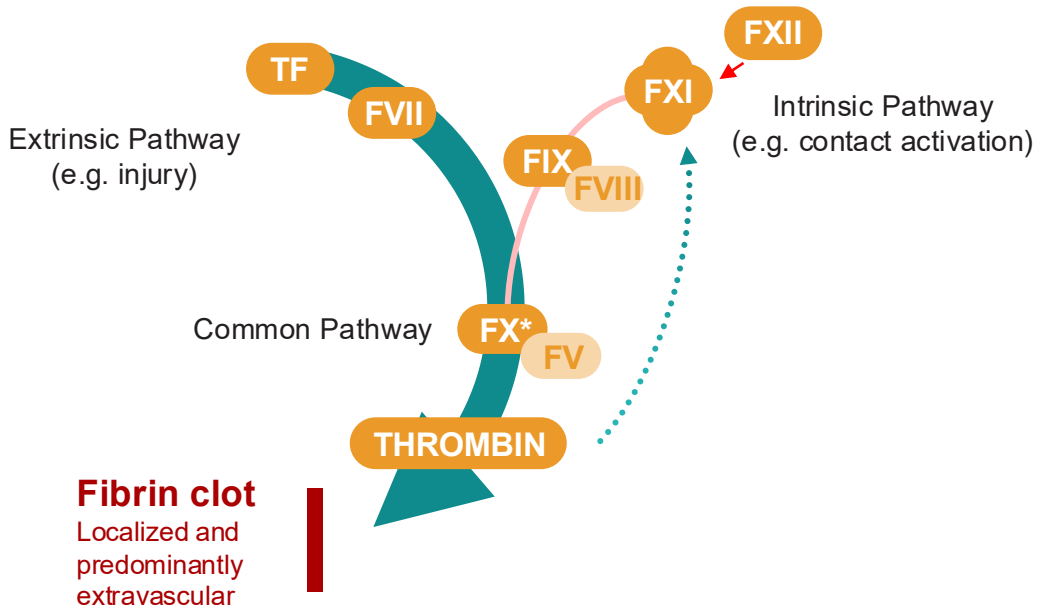
**Cancer-associated thrombosis**
~200,000[3]

[1] Addressable patient population in US; [2] Prevalence; [3] Annual incidence

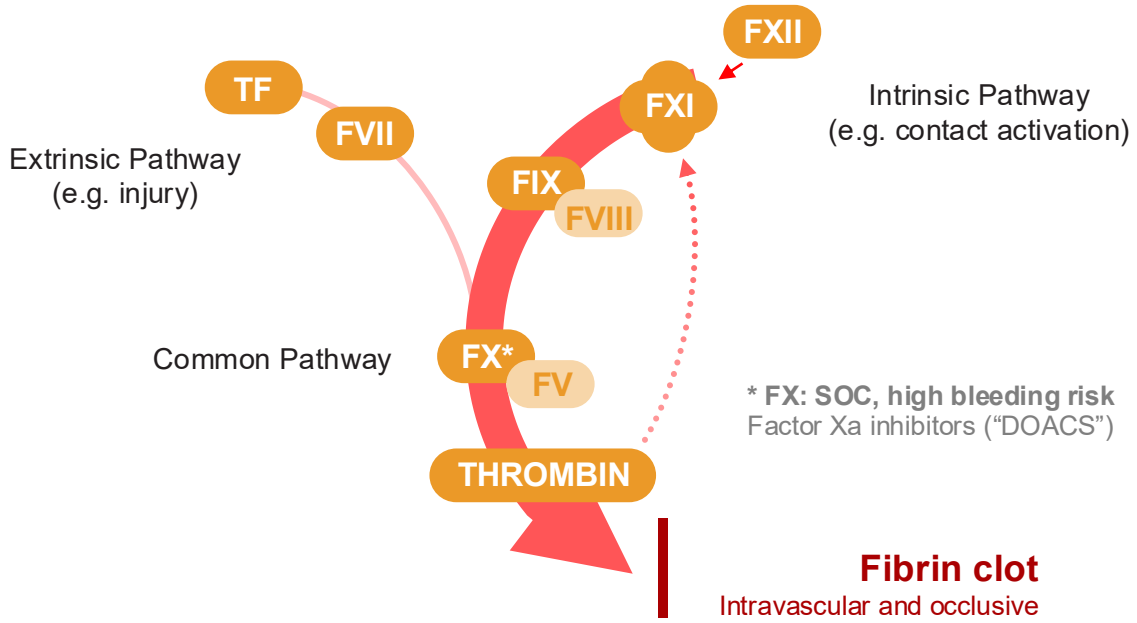
# FXI knockdown potentially inhibits thrombosis while sparing hemostasis

## Compelling target for thrombosis prevention without elevated bleed risk

### Hemostasis




### Thrombosis

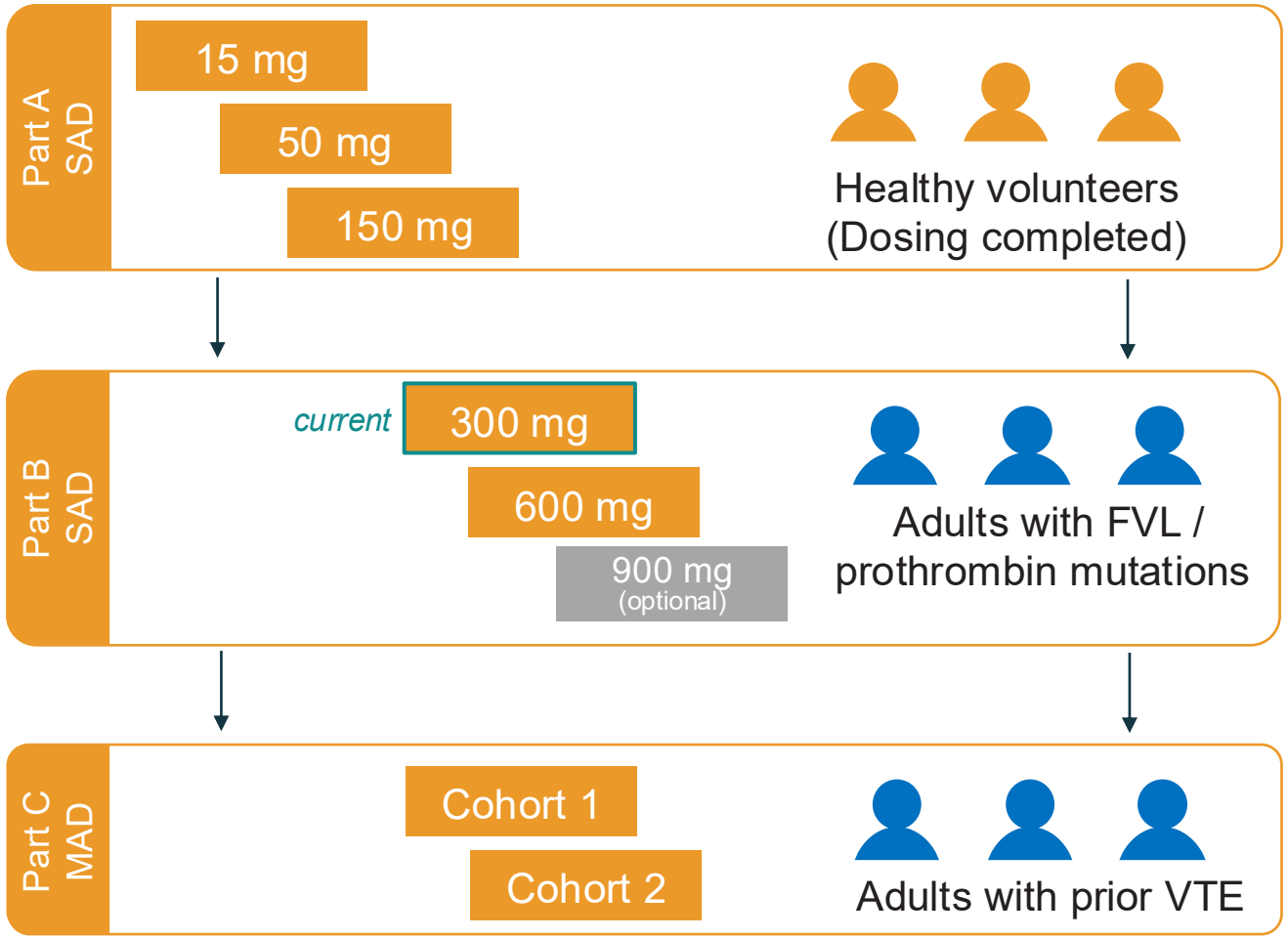



Low levels of FXI associated with protection from thrombosis ↓ ↑ High levels of FXI associated with a variety of thrombotic diseases

FIX: Factor IX; FV: Factor V; FVII: Factor VII; FVIII: Factor VIII; FX: Factor X; TF: Tissue factor.
Modified from Chan and Weitz, Arterioscler Thromb Vasc Biol. 2023.

# CITY-FXI Phase 1: Proof of biology in relevant patient population

**Ongoing Phase 1 with initial positive data; wide range of FXI knockdown data to support initiation of Phase 2**




Dose escalation subject to SRC approval

## Key Outcomes and Measures

**Primary**

- Safety and tolerability of a single dose of CITY-FXI

**Secondary**

- Characterize the pharmacodynamics (PD) effects of a single dose of CITY-FXI

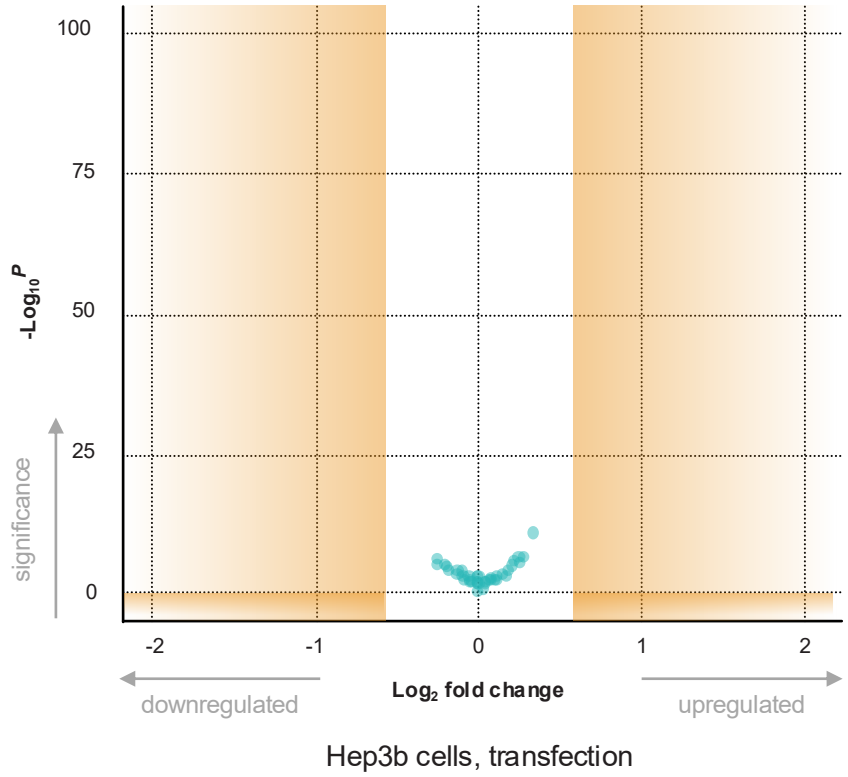
**Exploratory**

- Evaluate the effect of CITY-FXI on hemostasis biomarkers

FVL: Factor V Leiden

# CITY-FXI: Potent knockdown with no observed off-target effects

## No observed off-targets in preclinical studies

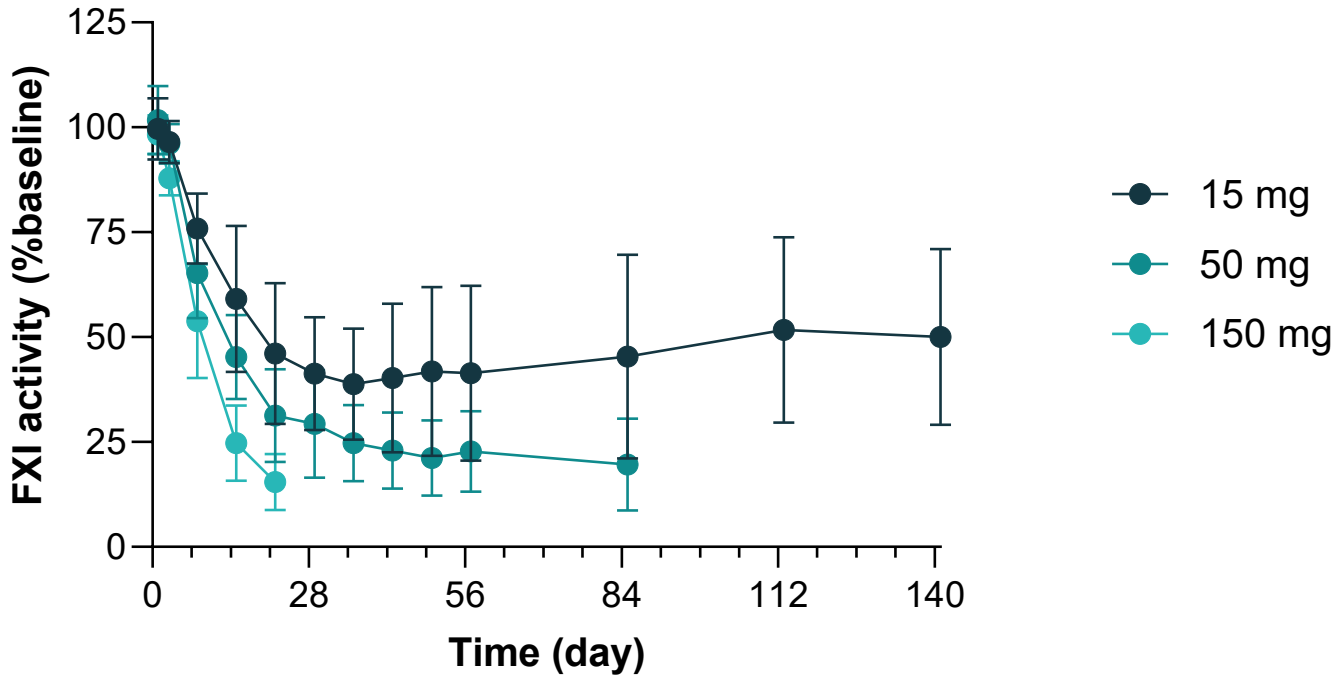



Hep3b cells, transfection

- Off-target activity is a potential driver of liver toxicity, including liver enzyme elevations
- CITY-FXI demonstrated a clean preclinical off-target profile, with no observed off-target transcriptional effects in a cell-based assay

# Potent FXI knockdown in humans with single subcutaneous dose

## CITY-FXI: 61%, 79% and 85% FXI knockdown at 15 mg, 50 mg and 150 mg respectively




Data: mean ± SD (n=6)

**Initial data support our goal of achieving a potential best-in-class profile**

# Clinical development plan supports evaluation in multiple indications

## PHASE 1

**Objectives**

- SAD and MAD study to investigate safety, tolerability, PK, PD
- Evaluate clinical proof of biology

**Part A**
SAD in healthy volunteers

**Part B**
SAD in FVL / PGM participants

**Part C**
MAD in prior VTE participants

## PHASE 2 Total Knee Arthroplasty (TKA)

**Objectives**

- Evaluate efficacy and safety in prevention of thrombosis
- Support initiation of Phase 3 studies in multiple indications (upon alignment with regulatory authorities)

## PHASE 3

**Objectives**

- Evaluate efficacy and safety to support regulatory approval
- Several Phase 3 studies are considered to seek approvals in multiple indications.

CITY-RBP4

# RNAi designed to transform treatment of Stargardt disease

# Blinding diseases with high unmet medical need

**Stargardt disease**

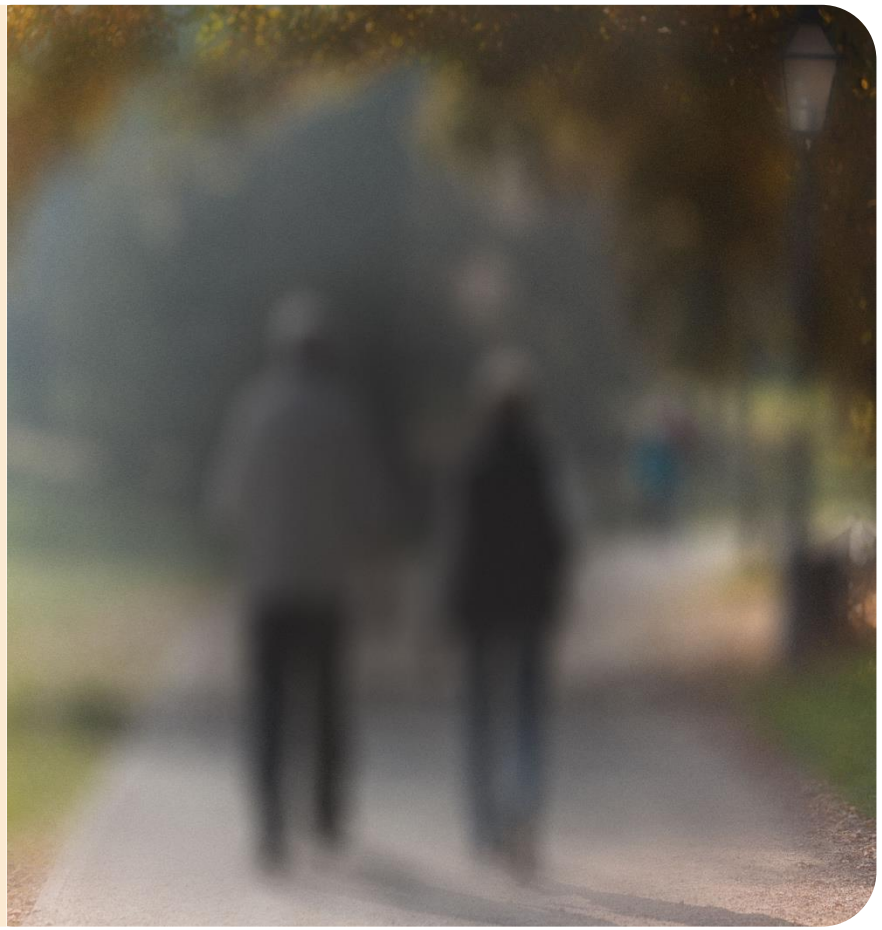
**Affects >30,000 people in U.S.**

- Most common inherited macular degenerative disease
- No approved therapies
- Typically begins in children and adolescents
- Most patients become legally blind in late 20s

**Geographic Atrophy (GA)**

**Affects ~ 1M people in U.S.**

- Advanced form of age-related macular degeneration
- Only two approved therapies with minimal benefit and invasive route of administration
- Common underlying mechanism with Stargardt disease



Vision loss is **progressive and irreversible** across both diseases

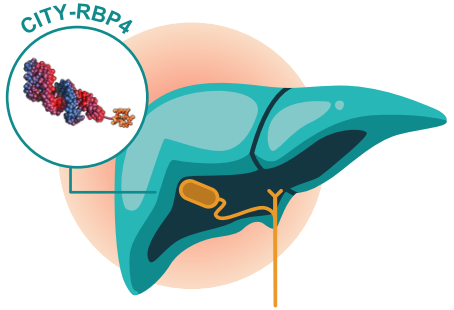
# RBP4: RNAi for Stargardt disease

## Limiting vitamin A delivery is an established pathway to slow vision loss

RBP4 is main vitamin A carrier from liver to eye




ABCA4 mutations cause buildup of toxic vitamin metabolites




CITY-RBP4 designed to silence hepatic RBP4, reducing vitamin A delivery to the eye

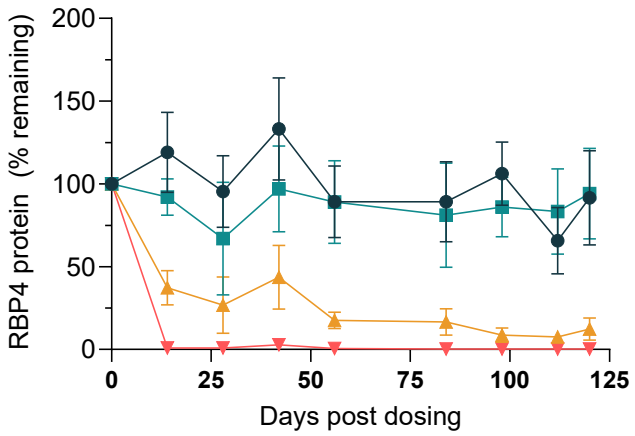



Reducing vitamin A potentially prevents toxic accumulation and vision loss

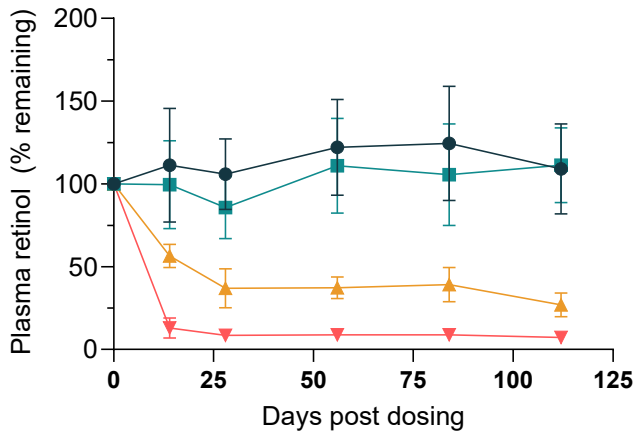
# Reduction of ocular A2E observed in Stargardt model

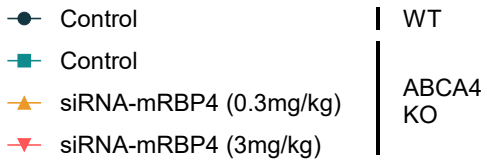
## Normalization to wildtype levels of A2E observed in Stargardt mice (ABCA4$^{-/-}$) treated with RBP4 knockdown

### Plasma RBP4 protein

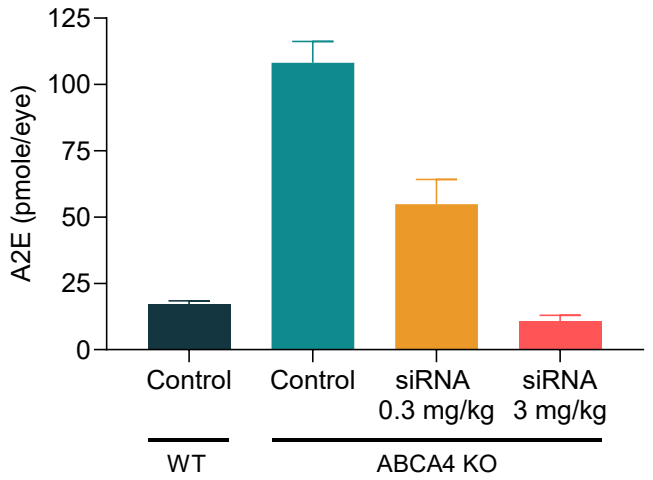



### Plasma vitamin A




### Eye toxic vitamin A metabolite
(after 4 months of treatment)



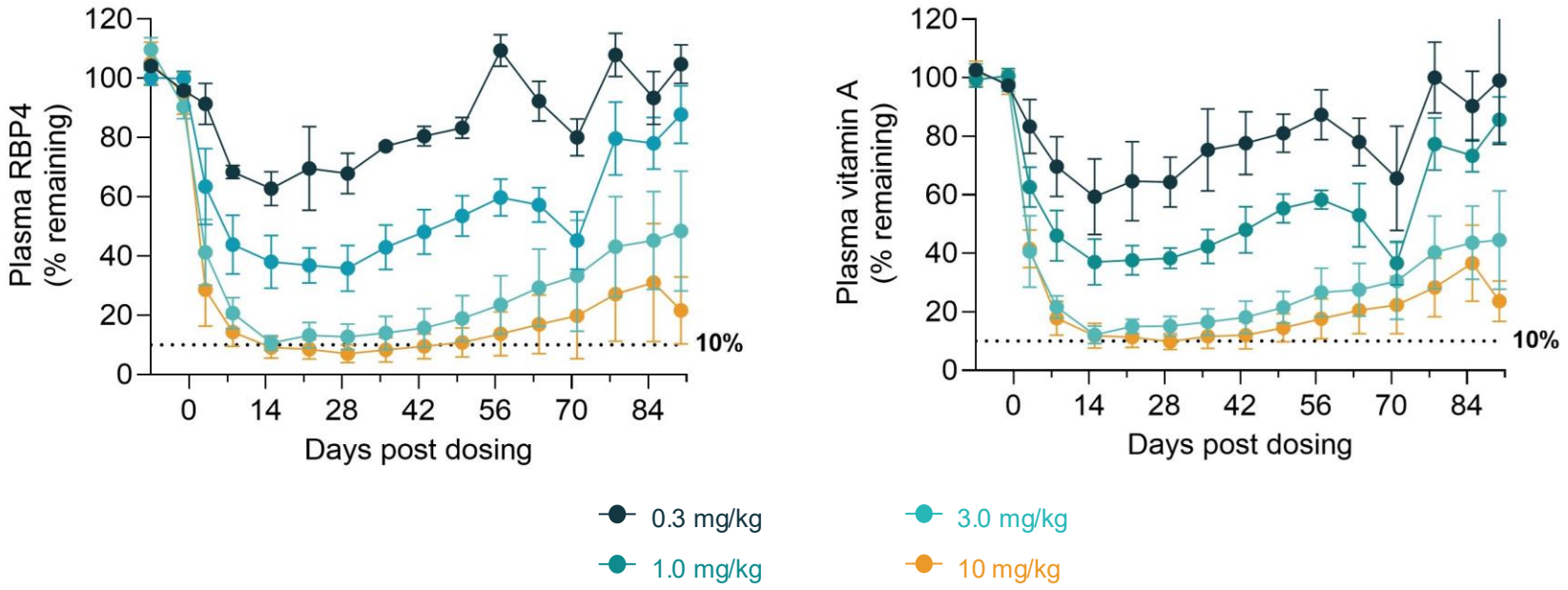

A2E is predominate toxic vitamin A metabolite

A2E: N-retinylidene-N-retinylethanolamine (toxic vitamin A metabolite)

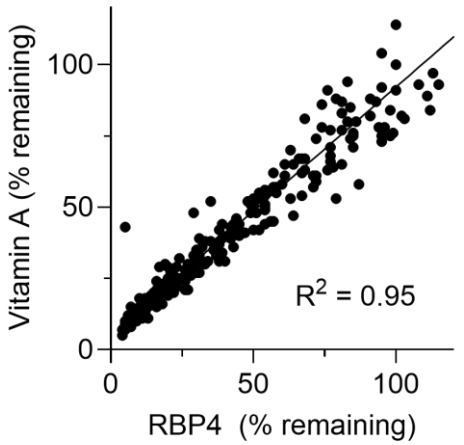
# Potent and durable suppression observed in NHPs treated with CITY-RBP4

**Long duration suggests potential for quarterly to biannual subcutaneous dosing in humans**

## >90% RBP4 and vitamin A suppression at 3 mg/kg

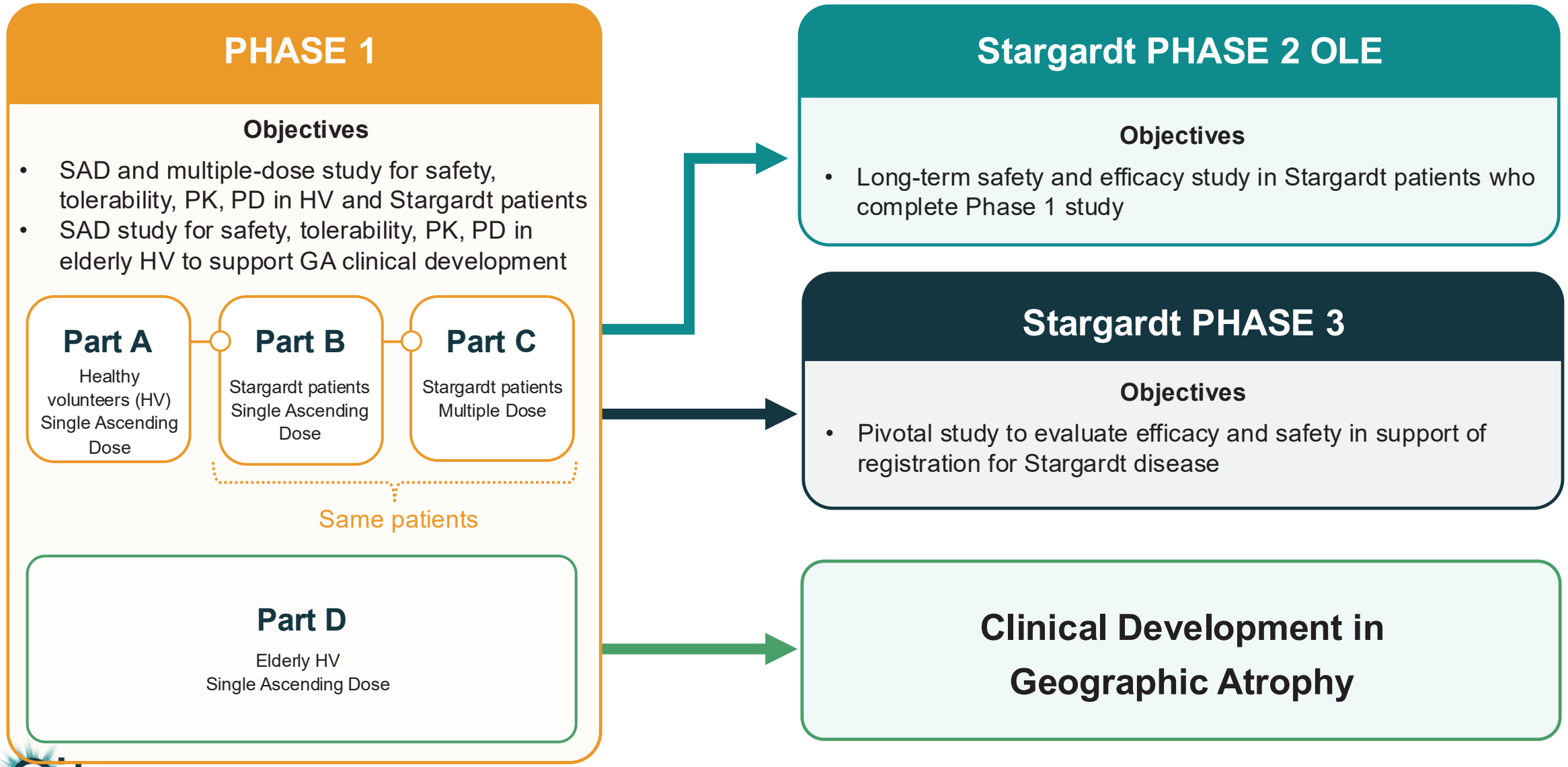



## 1:1 correlation between RBP4 and vitamin A




**Phase 1 study ongoing**

# Clinical development plan for Stargardt disease and GA




OLE: Open label extension

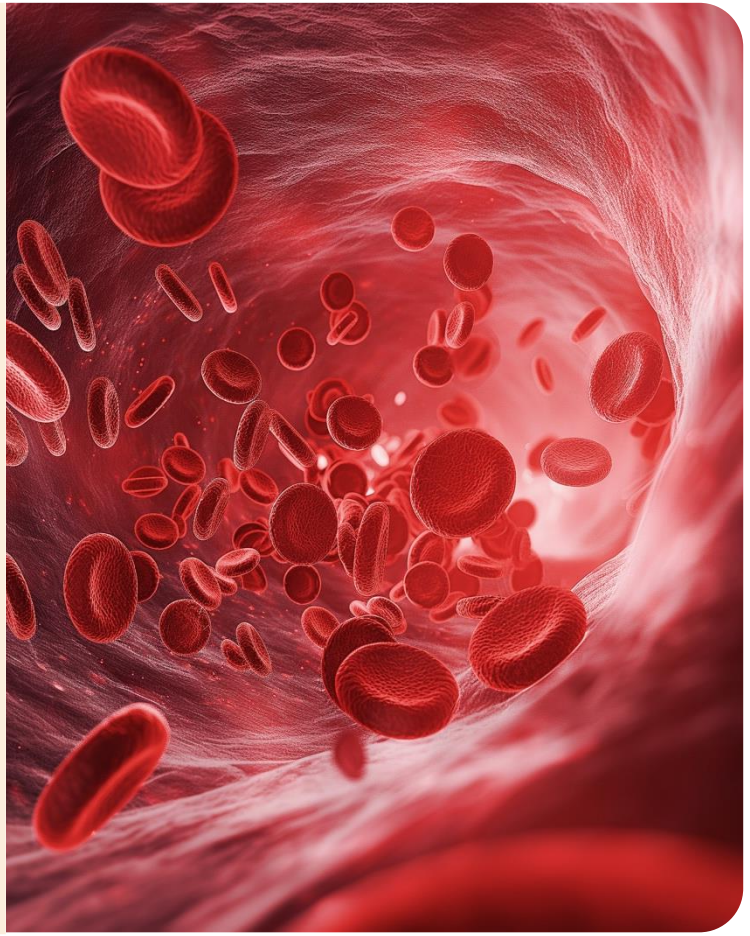
CITY-TFR2

# RNAi designed to provide safe and effective treatment of anemia

# Significant unmet need in anemia of chronic disease (ACD)

**Affects >5 million people in U.S.**

- Comprises up to 40% of all anemias
- Drives significant morbidities across spectrum of chronic conditions
- Characterized by iron restriction, meaning iron is present but not available to produce red blood cells
- Current therapies (ESA and HIF-PH inhibitors) come with significant safety and efficacy limitations
- Patients experience persistent fatigue, diminished quality of life, and many become transfusion dependent, which is highly burdensome and can lead to serious medical complications

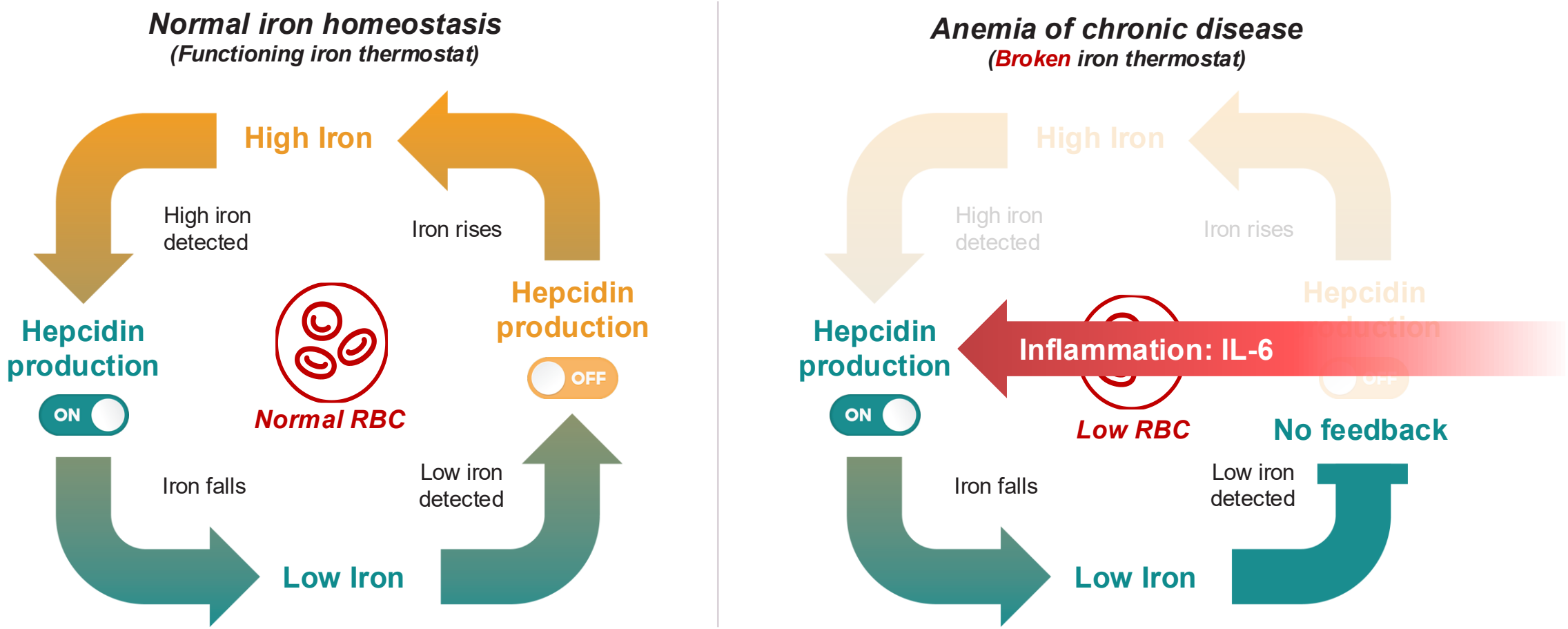


**Our initial focus is anemia of myelofibrosis, with potential expansions into inflammatory bowel disease, chronic kidney disease and more**

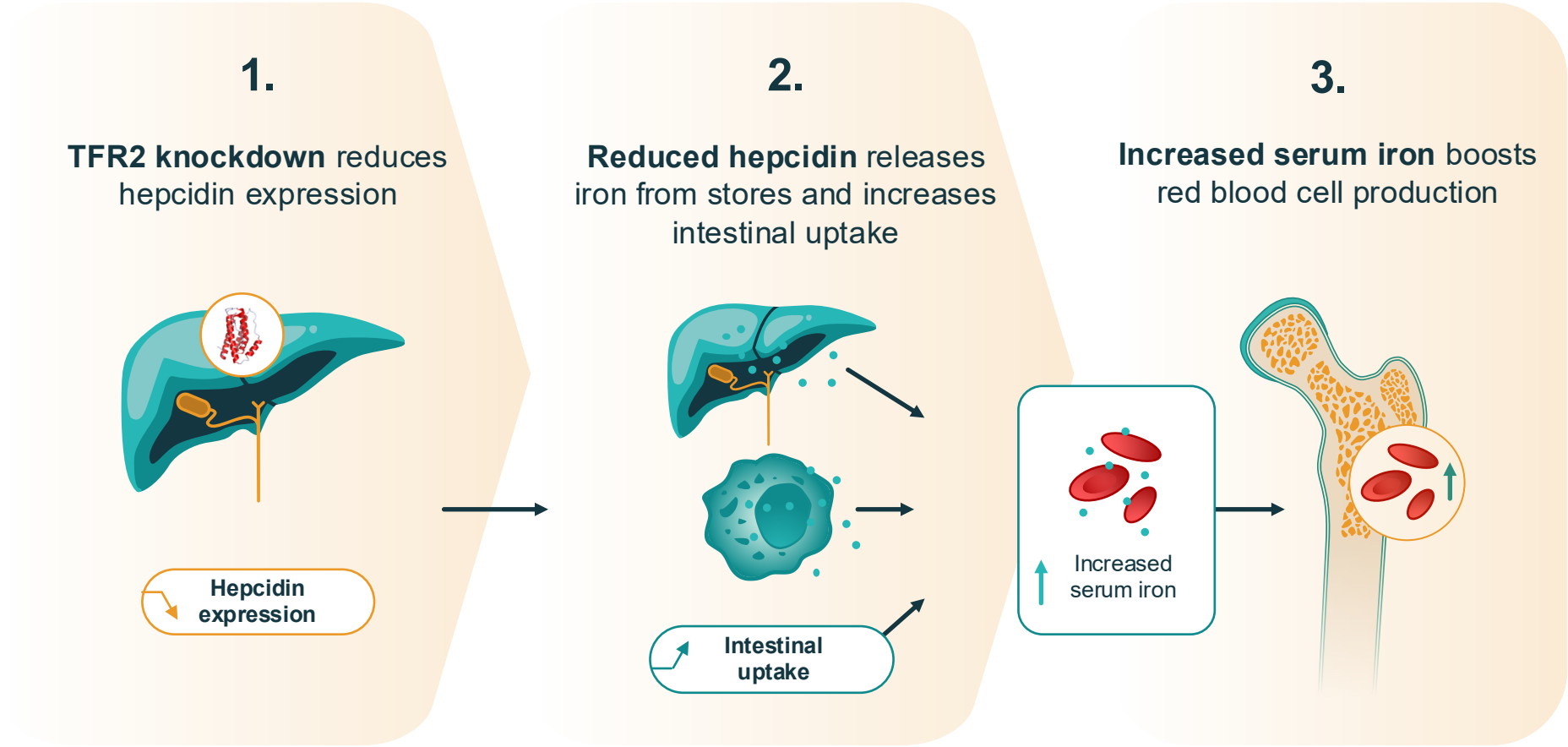
ESA, Erythropoiesis-Stimulating Agents; HIF-PH, Hypoxia-Inducible Factor Prolyl Hydroxylase

# ACD short-circuits the body's iron thermostat

**Iron homeostasis requires feedback between liver and bloodstream through hepcidin**

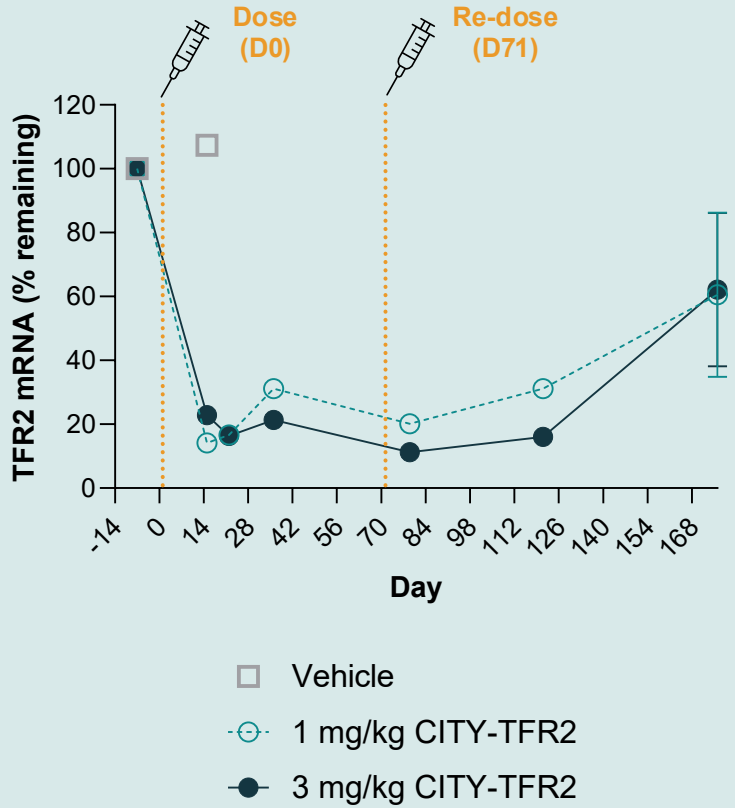


# TFR2 knockdown as potentially optimal mechanism to treat ACD

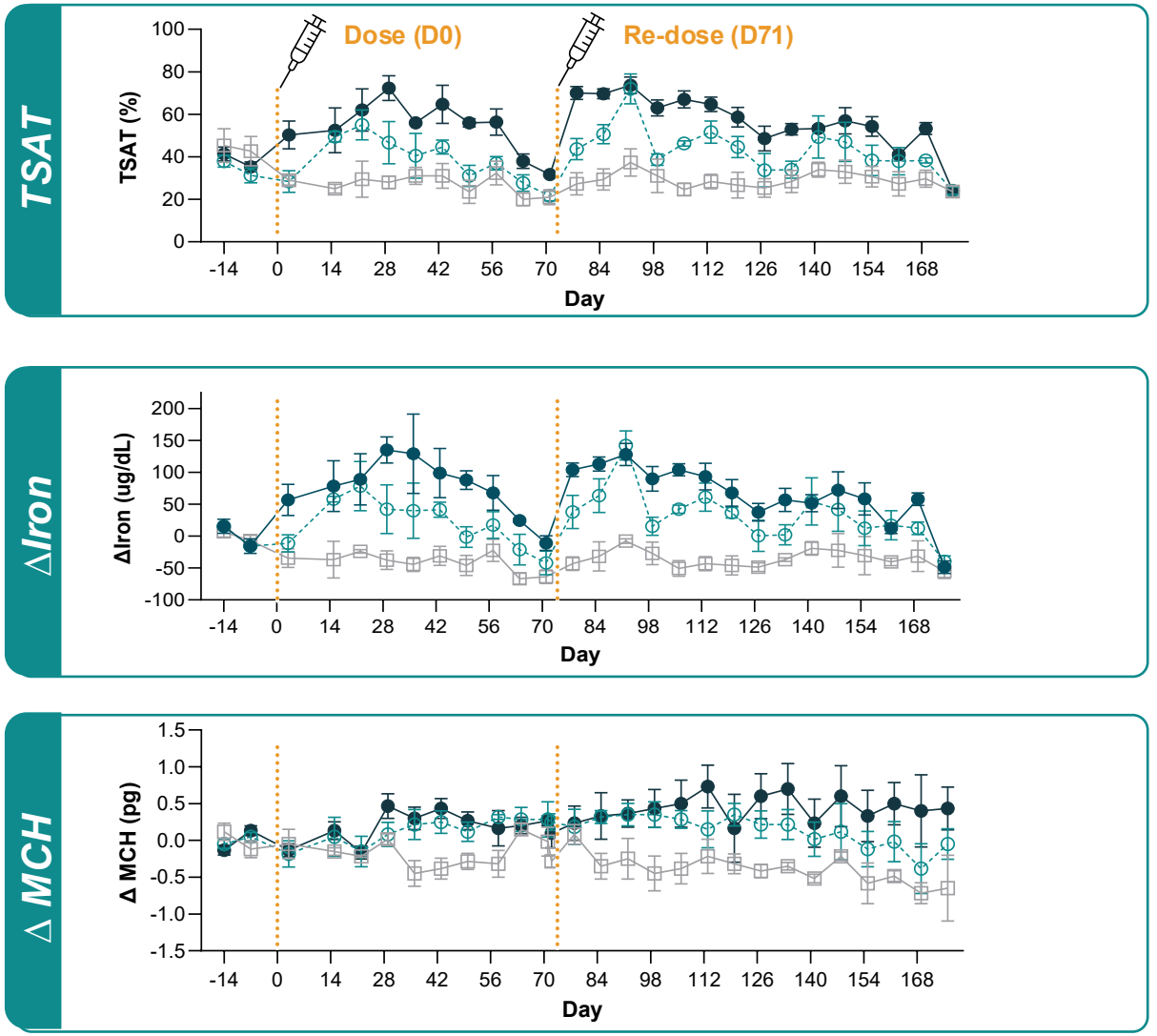



**Humans with loss-of-function mutations in TFR2 characterized by low hepcidin and high iron**

# Suppression of TFR2 increased iron, TSAT and MCH in NHP




TSAT: transferrin saturation, MCH: mean corpuscular hemoglobin
TFR2 mRNA knockdown from sparse sampled liver biopsies across NHPs



# Clinical development plan focused on myelofibrosis (MF), with potential expansion to additional indications

## Investigator-Initiated Trial (IIT) in MF

**Objectives**

- Leverage IIT in China to quickly obtain data from patients
- First-in-human single and multiple doses in MF patients
- Evaluate safety, tolerability, PK/PD and clinical PoC for improvement of anemia, along with markers of systemic iron availability

## PHASE 1/2 in MF

**Objectives**

- Evaluate safety, tolerability, PK, PD and efficacy data (e.g. Hb) in healthy volunteers and broader MF patient population
- Support initiation of Phase 2 in additional indications for anemia of chronic diseases (e.g. IBD, CKD, others)

## Phase 3 in MF

**Objectives**

- Pivotal study to evaluate efficacy and safety in support of registration for treatment of anemia in MF

## Clinical Development in Additional Indications

The City Platform

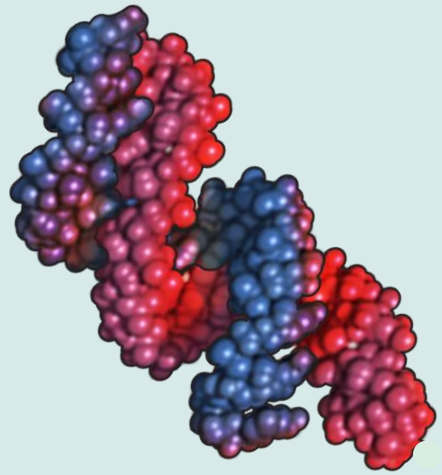
# Next-generation RNAi engineering

# cityRNA: Unlocking the next generation of RNAi therapeutics

**A structurally distinct class of trigger molecules designed to perform where canonical approaches fall short**

- Improved biophysical properties designed to address challenges of extrahepatic delivery
- Only trigger that productively engages both AGO2 and AGO3, providing potential for enhanced silencing efficiency, to our knowledge
- Designed to improve specificity, potentially creating wider therapeutic window
- Increased design flexibility, expanding landscape of triggers per target
- Anticipated lower cost of goods and more scalable manufacturing
- Broad, defensible platform IP

**30% shorter and less charged than siRNA triggers**

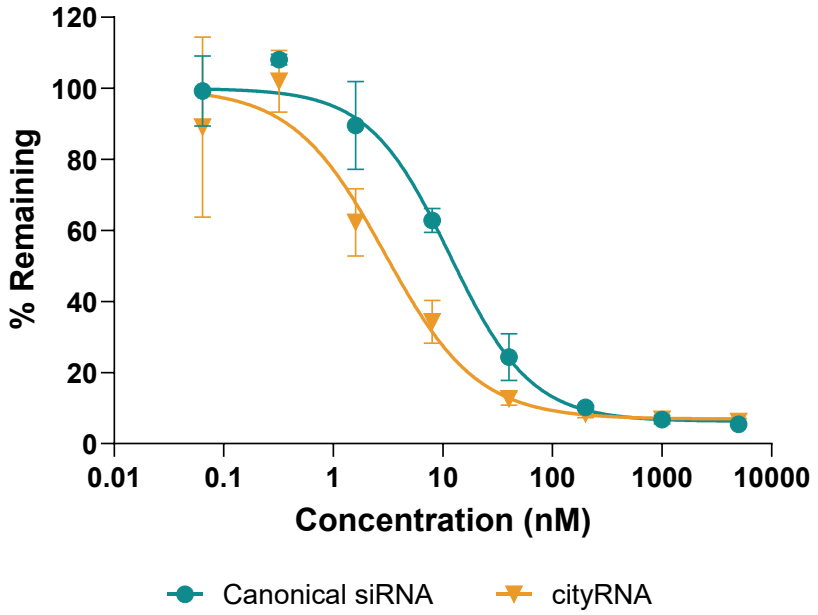


AGO2: Argonaute2 catalytic enzyme of RNA-induced silencing complex (RISC); AGO3: Argonaute3 catalytic enzyme of RISC

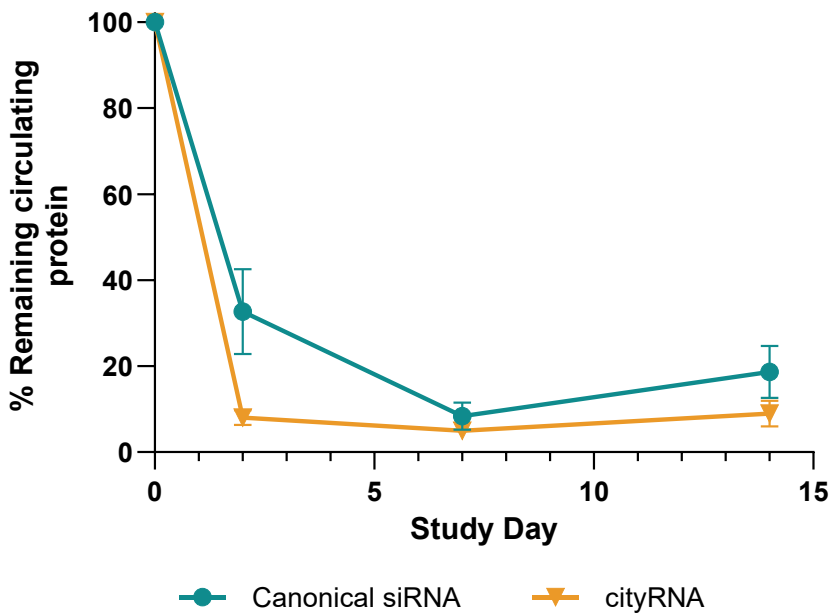
# cityRNA design outperformed canonical siRNA

## Comparison of seed matched cityRNA with canonical siRNA in vitro and in vivo

### Improved potency in vitro with cityRNA design
**Free uptake in primary human hepatocytes**

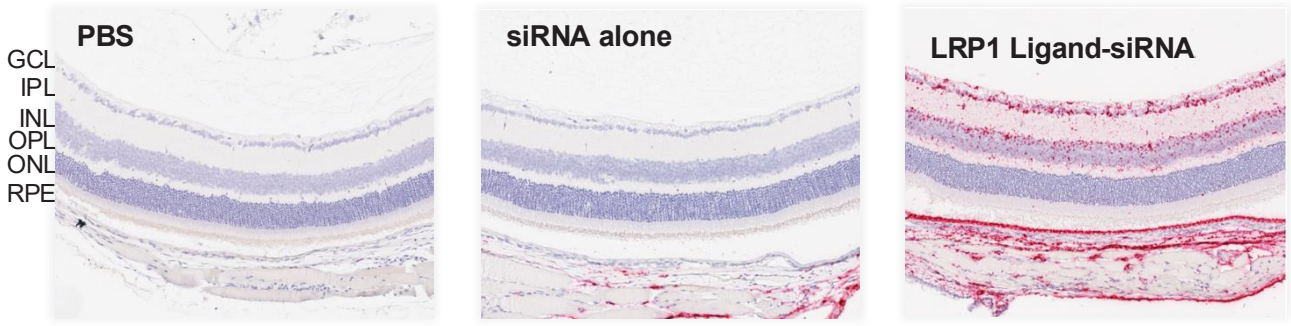


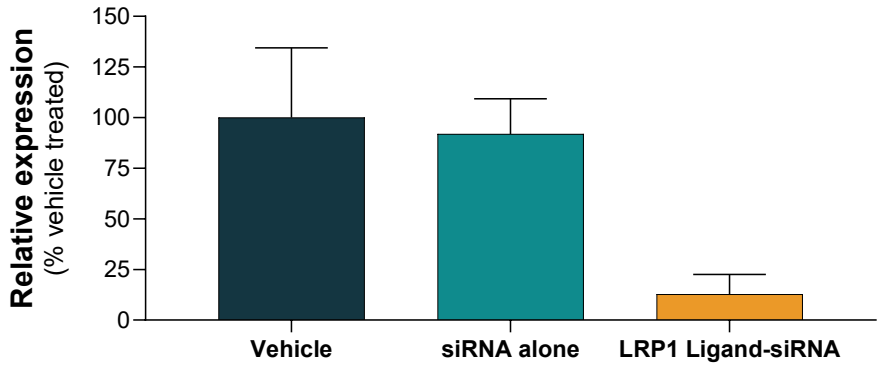

### Faster onset and deeper knockdown in vivo for cityRNA
**Single 3 mg/kg subcutaneous dose in mice**



# Broad distribution and robust target knockdown with proprietary ligand

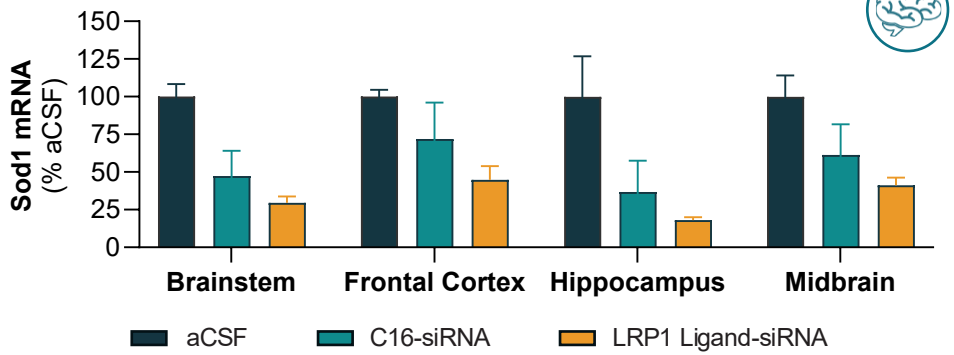
## Mouse retina



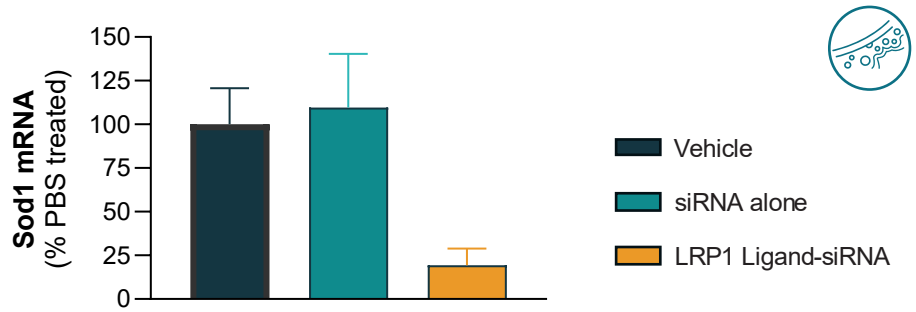

Top: 1µg siRNA IVT in mouse eye, miRNAscope 10 days post-dose
Bottom: target knockdown after intravitreal injection of 9 µg Ligand-siRNA in mouse eye

## Rat brain




Sod1 mRNA expression 14 days post 200 µg IT dose in rat

## Mouse adipose




Sod1 mRNA expression 14 days post single IV dose

Retinal cell layers (top to bottom): GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; RPE, retinal pigment epithelium. aCSF, artificial cerebrospinal fluid.

# Partnerships and upcoming milestones

# Strategic partnerships to advance extrahepatic RNAi therapeutics

**Leverage potential of the City Platform, while preserving our ability to pursue additional targets in the eye and CNS**

BAUSCH + LOMB

**$15M upfront (cash and convertible note[1])**
**Additional consideration up to $485M plus tiered royalties**

- Focused on developing a novel RNAi therapy for treatment of retinal diseases, including GA
- Leverages our next-generation ligand delivery technologies to enable intravitreal administration
- Directed against a specific disease target
- Expect Bausch + Lomb to select a development candidate by year-end 2026

Biogen

**$46M upfront (cash and convertible note[1])**
**Additional consideration up to $1B plus tiered royalties**

- Focused on developing a novel systemic RNAi therapy for certain CNS diseases
- Combines our RNAi trigger engineering capabilities with Biogen's proprietary drug delivery technology
- Initially focused on a single target, with an option to designate one additional target
- Expect Biogen to select a development candidate by year-end 2027

City THERAPEUTICS

[1] Notes converted into shares of common stock in connection with our IPO

# Multiple anticipated clinical milestones

| | 2026 | | 2027 | | 2028 |
|---|---|---|---|---|---|
| | LATE | EARLY | MID | LATE | EARLY |
| **CITY-FXI** | **Phase 1** additional data | | **Phase 1** SAD data<br>**Phase 2** TKA trial initiation | **Phase 1** MAD data | **Phase 2** TKA data |
| **CITY-RBP4** | ✓ **Phase 1** trial initiated | | **Phase 1** initial data | **Phase 2** GA trial initiation | **Phase 1** SAD/MAD data |
| **CITY-TFR2** | **IIT** initiation & **IND** filing | **Phase 1/2** trial initiation | **MF IIT** data | **Phase 1/2** data | **Phase 2** trial initiation |
| **PARTNERSHIPS** | B+L Development candidate | | | Biogen Development candidate | |

All milestone timings are preliminary and subject to change. Early defined as Q1-Q2, mid as Q2-Q3 and late as Q3-Q4.
IND: Investigational New Drug Application or equivalent

## Vision

Lead the next generation of RNAi therapeutics

## Mission

Improve patients' lives through breakthrough RNAi science, building a leading biopharmaceutical company with enduring impact

City THERAPEUTICS