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Corporate Deck

Restoring Balance to Life with Transformative Therapies

February 2023

Forward Looking Statements

Statements in this presentation that are not descriptions of historical facts are forward-looking statements relating to future events, and as such all forward-looking statements are made pursuant to the Securities Litigation Reform Act of 1995. Statements may contain certain forward-looking statements pertaining to future anticipated or projected plans, performance and developments, as well as other statements relating to future operations and results. Any statements in this presentation that are not statements of historical fact may be considered to be forward-looking statements. Words such as "may," "will," "expect," "believe," "anticipate," "estimate," "intends," "goal," "objective," "seek," "attempt," or variations of these or similar words, identify forward-looking statements.

These forward-looking statements by their nature are estimates of future results only and involve substantial risks and uncertainties, including but not limited to risks associated with the uncertainty of clinical trial results, future financial results, additional financing requirements, development of new products, the impact of competitive products or pricing, technological changes, the effect of economic conditions and other uncertainties detailed from time to time in our reports filed with the Securities and Exchange Commission.

Our actual results may differ materially from expectations based on the above factors and other factors more fully described in our public filings with the U.S. Securities and Exchange Commission, which can be reviewed at www.sec.gov.

Two Clinical Stage Programs with Transformative Therapies Targeting Diseases of Dysglycemia

RZ358 for Congenital Hyperinsulinism (HI)

- Congenital HI is over-production of insulin resulting in life-threatening hypoglycemia and neurologic damage
- RZ358 is a fully humanized monoclonal antibody, works downstream from the pancreas, binds to the insulin receptor at a non-competitive site (not an antagonist) and agnostic to genetic causes
- Open-label Phase 2b study results demonstrated up to ~75% improvement in hypoglycemia at the 6 mg/kg and 9 mg/kg cohorts (the expected therapeutic doses), topline results presented in 2Q 2022
- Interactions with Health Authorities planned for in 2H 2022, Phase 3 start anticipated in 1H 2023
- Orphan designation in US and EU, Pediatric Rare Disease designation
- Potential for expanded indications: post bariatric surgery hypoglycemia, insulinoma

RZ402 for Diabetic Macular Edema (DME)

- Microvascular complication of diabetes results in breakdown of the blood-retinal barrier and eventual blindness
- Potent, selective small molecule kallikrein inhibitor
- Oral therapy offering the potential to treat DME earlier and to address the disease at the vascular source
- Phase 1 program complete and demonstrated good bioavailability, with drug levels that safely exceeded target efficacious concentrations, supporting potential for once daily dosing
- Initiated Phase 2 proof-of-concept study in 4Q 2022; topline data expected by 1Q 2024
- Potential for expanded indications: diabetic retinopathy, hereditary angioedema, systemic inflammatory syndromes and others

Cash balance as of 4Q22 anticipated to fund the next two trials for both, RZ358 and RZ402

Leadership with Deep Expertise in Metabolic Drug Development

Nevan Charles Elam, JD
Founder & CEO

- SAVARA
- Aerogen
- NEKTAR
- HARVARD UNIVERSITY

Brian Roberts, MD
Chief Medical Officer

- FibroGen
- CYMABAY
- STANFORD UNIVERSITY
- GEORGETOWN UNIVERSITY

Michael Covarrubias
Head of Portfolio Management

- Seagen
- AMGEN
- Genentech — A member of the Roche Group
- INDIANA UNIVERSITY

Erin O'Boyle
Head of Clinical Operations

- FibroGen
- HERON THERAPEUTICS — Developing Best-in-Class Medicine. Improving Lives.
- LUX ET SPES STONEHILL COLLEGE

Michael Deperro
Head of Corporate Development

- Patheon
- MERCK
- Alkermes
- UNIVERSITY OF NOTRE DAME

Davelyn Eaves Hood, MD
Scientific & Patient Affairs

- CHI Congenital Hyperinsulinism International
- HI GLOBAL REGISTRY
- aetna
- UTHealth — The University of Texas Health Science Center at Houston

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RZ358

A MONOCLONAL ANTIBODY ENTERING PHASE 3 CLINICAL DEVELOPMENT FOR CONGENITAL HYPERINSULINISM

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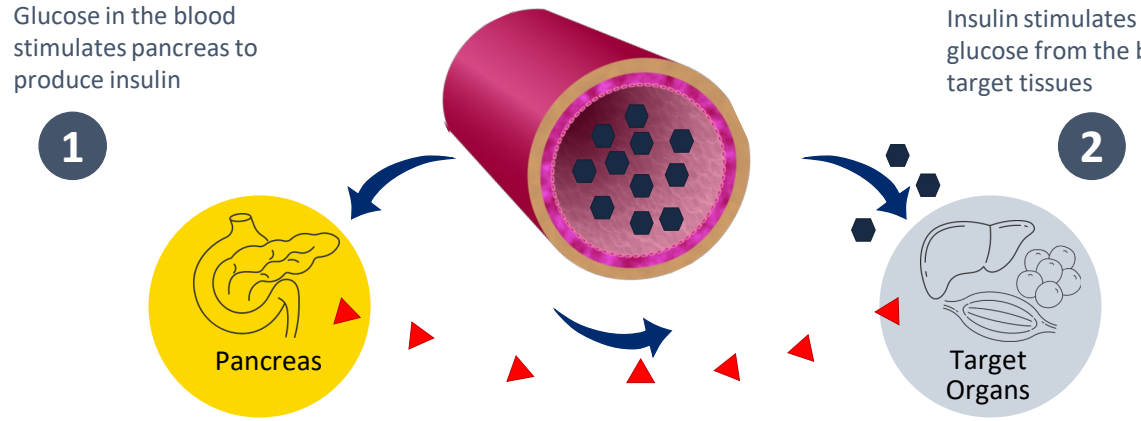
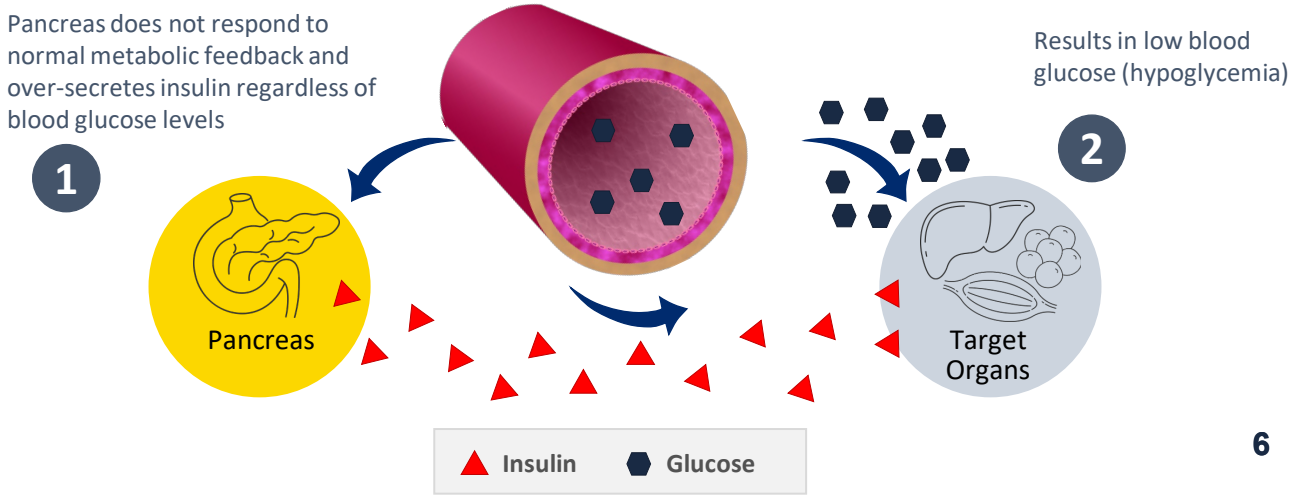
Congenital HI Disease State

- Ultra-rare disease
- 1 in 33,000 live births
  - Less than 10,000 in US and EU each
- Excessive insulin secretion from pancreatic beta cells regardless of blood sugar levels
- Most common cause of persistent hypoglycemia in infants and children
  - Brain (highly dependent on glucose as its main fuel source) is starved of energy
  - Symptoms often not recognized until life-threatening
  - Risk of neurological complications, coma, and death
- Current SOC are suboptimal due to side effects and significant persistent hypoglycemia

Normal Insulin-Glucose Feedback Loop



Congenital HI



Congenital HI Standard of Care is Suboptimal

- No FDA-approved therapy addresses all forms of Congenital HI

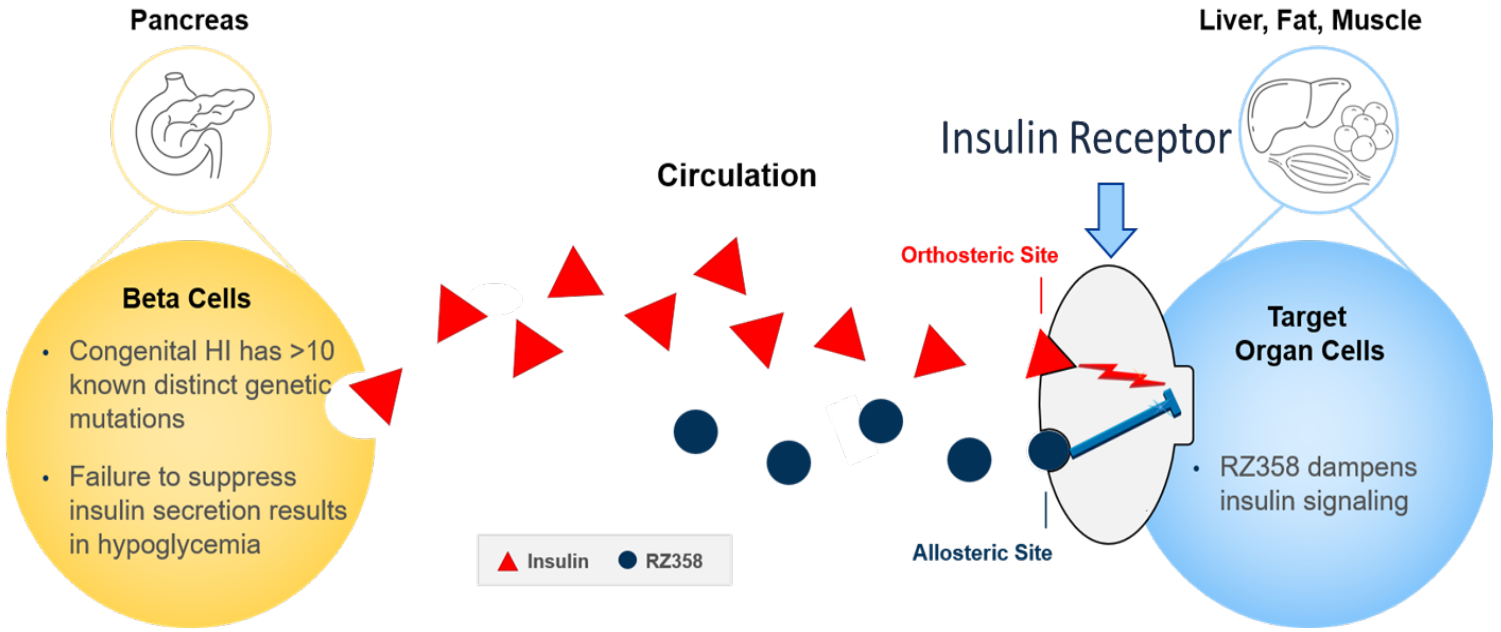
Glucagon	Diazoxide	Somatostatin Analogues	Pancreatectomy
Opposes insulin's actions	***K_{ATP} channel agonist***	***Octreotide/Lanreotide***	***Resection for diffuse disease***
— Current formulations short-acting	— Ineffective in 50% of patients (with K_{ATP} mutations)	— Effects wane with repeat doses	— Invasive procedure, not done globally
— Temporary measure for emergent glucose correction	— FDA warning for pulmonary hypertension	— Marginal efficacy	— Hypoglycemia may persist for years in up to half of patients
— Repeated use may deplete liver glucose stores	— Fluid retention affecting heart/lungs	— Gastrointestinal side effects	— Requires adjuvant medical management, and/or repeat surgery
— Long-term efficacy is modest	— Facial changes and excessive hair growth	— Risk of necrotizing enterocolitis particularly in newborns	— Eventually insulin therapy required
		— Potential interaction with pituitary hormones (growth and thyroid)	***Resection for focal disease***
			— Limited number of overall cases
			— Only done at specialized centers
			+ Can be curative for patients

RZ358: Monoclonal Antibody Product Candidate Being Developed for Congenital HI

- Fully humanized monoclonal antibody, works downstream from the pancreas and agnostic to genetic causes
- Mechanism of Action (MOA) is uniquely suited for Congenital HI: antibody developed specifically for the disease
  - Binds to the insulin receptor at a non-competitive site (not an antagonist), normalizing insulin activity to prevent hypoglycemia
  - Normalized insulin activity protects against hyperglycemia
  - Highly selective to the insulin receptor (does not bind to the IGF-1 receptor)
  - Dose dependent pharmacokinetics with a half life greater than 2 weeks

RZ358: Novel Mechanism for the Treatment of Hyperinsulinism

- Humanized IgG2 monoclonal antibody
- Negative Allosteric Modulator: reversibly counteracts insulin at a distinct site at the Insulin Receptor
  - Discovered and developed specifically for hyperinsulinism
  - Downstream from pancreas, not genetics-dependent
- Administered as 30 min IV infusion every 2 weeks
- Clinical experience in 80+ participants: favorable PK/PD, no safety signals to date
- Phase 2b (RIZE) study data available



RZ358 MOA: Potential for Universal Treatment for all Forms of Congenital HI

	Current Standard of Care	RZ358
Targeting	− Beta cells only	+ Insulin receptor/signal on insulin-dependent target organs
Development	− Not developed for Congenital HI	+ Tailored for Congenital HI
Impact	− Marginally effective, invasive, and/or significant AEs	+ Normalizes insulin activity for optimal glucose range
Relevancy	− Genetics-dependent narrow targeting	+ Potentially universal treatment

Completed Clinical Studies Demonstrate Proof-of-Concept

PHASE 2a:

- RZ358 administered to Congenital HI patients with a range of glucose values between normal and severely hypoglycemic
  - Subjects with hypoglycemia restored to normal range
  - Subjects with normal blood glucose levels remained the same
    - No evidence of hyperglycemia
  - Effect persisted for 4 weeks, consistent with PK/PD observed in Phase 1
  - Safe and well-tolerated
  - Established proof of concept
  - Informed Phase 2b entry criteria and endpoints

PHASE 2b:

- Study was conducted primarily in a young pediatric population: average ~6.5 years of age
  - Diverse group of patients in the study across gender and genetics
  - Add-on to SOC therapies
    - RIZE again showed that SOC therapies are suboptimal for some CHI patients
    - Patients enrolled had an average of ~25% time in a hypoglycemic range at baseline
- RZ358 demonstrated:
  - ~50% improvement in hypoglycemia across all doses and cohorts
  - ~75% improvement in hypoglycemia at the 6 mg/kg and 9 mg/kg cohorts
    - These are the likely two dosing levels to be studied in Phase 3
- RZ358 was generally safe and well-tolerated
- Expected RZ358 concentrations achieved
- Dose and exposure-dependent responses were observed
  - 100% patient response rate with > 50% Hypoglycemia correction at the top dose

Phase 2a: RZ358 Brings Congenital HI Patients into Glucose Target Range

Design

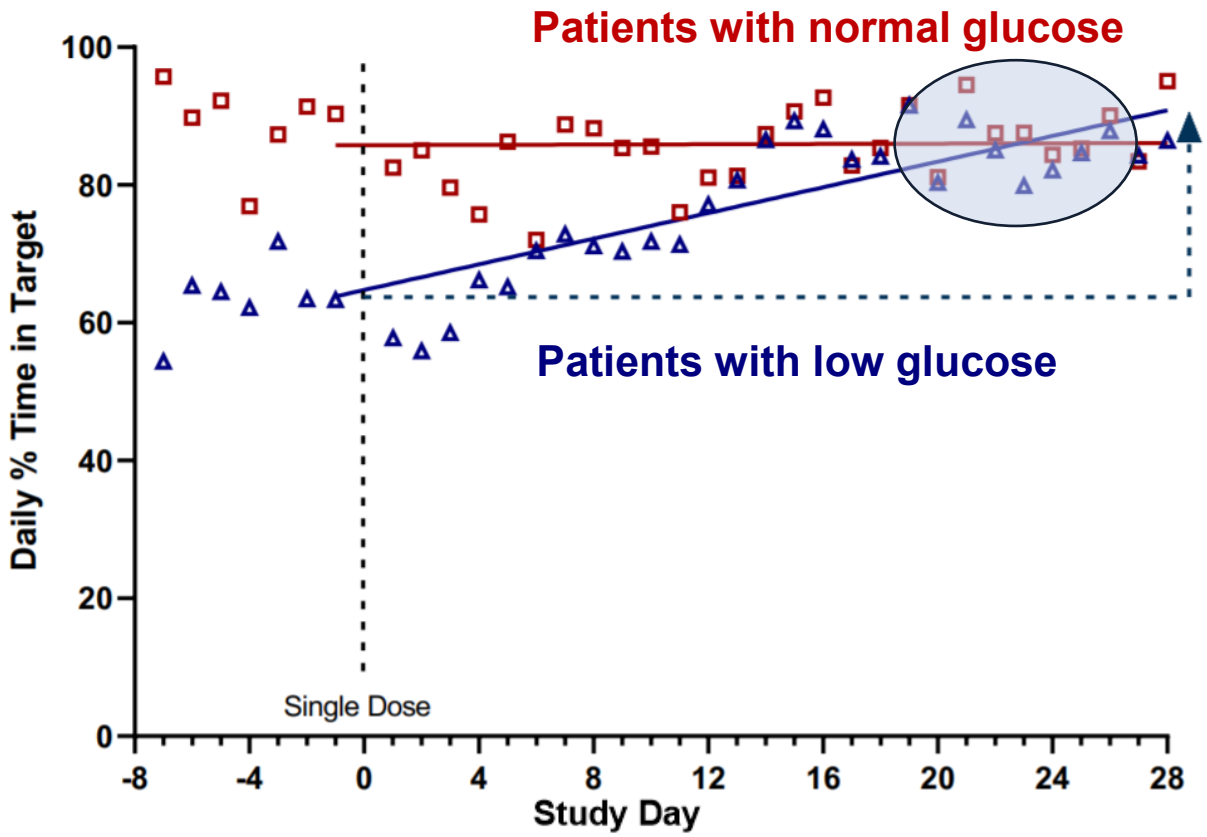
- Single IV doses of 1 to 9 mg/kg in patients with congenital hyperinsulinism
- 14 patients; ages ≥ 12 in Europe and ≥ 18 in the US
- Congenital hyperinsulinism patients by subgroup:
  - hypoglycemic at baseline (n=9)
  - normal baseline glucose (n=5)

Results

After a single dose of RZ358:

- Group with baseline hypoglycemia (n=9) achieved glucose normalization by 2 weeks
  - Equating to a 50% improvement from study baseline
- No hyperglycemia in patients with normal baseline glucose (n=5)
  - Confirmation of mechanism of action
- Effect persisted for 4 weeks, consistent with Phase 1 PK/PD
- Safe and well-tolerated
- Establishes proof of concept
- Informed Phase 2b entry criteria and endpoints

Time in Glucose Target Range (70-180 mg/dL) by CGM*



Glucose normalization achieved after two weeks with single dose of RZ358 in Congenital HI patients

**Phase 2b (RIZE) study primary endpoint*

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Phase 2b RIZE Study Overview and Results

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RIZE Study Summary

- Study was conducted primarily in a young pediatric population: average ~6.5 years of age
  - Diverse group of patients in the study across gender and genetics
  - Whether on SOC therapies, patients had to have substantial hypoglycemia to be enrolled
    - Patients enrolled had an average of 25% time in a hypoglycemic range at baseline
- RZ358 demonstrated:
  - ~50% improvement in hypoglycemia across all doses and cohorts
  - ~75% improvement in hypoglycemia at the 6 mg/kg and 9 mg/kg cohorts
- RZ358 was generally safe and well-tolerated
- Expected RZ358 concentrations achieved
- Dose and exposure-dependent responses were observed
  - 100% patient response rate with > 50% Hypoglycemia correction at the top dose

Topline Glycemic Results: Far Exceeded Expectations

- Low starting dose (3 mg/kg) was selected for safety with minimal expectations for efficacy
  - Notably, an improvement in hypoglycemia of ~25% was achieved
- Improvements in hypoglycemia of ~75% at the mid (6 mg/kg) and top doses (9 mg/kg) and a high patient response rate
  - Improvements were comparable between both BGM (hypoglycemia events) and CGM (hypoglycemia time)
- Better than expected hypoglycemia correction resulted in an increase from baseline in mild, self-limiting, non-clinically meaningful hyperglycemia in patients taking background therapies
  - TIR (70-180 mg/dL) by CGM improved 8% across all doses, 16% at the top dose, and more significantly (>25%) in patients without baseline hyperglycemia on SOC
- Clear dose-response observed
- Results demonstrate that RZ358 can be administered at fixed dose levels with the potential to be an effective combination or monotherapy in all patients with congenital and syndromic HI

RZ358-606 (RIZE) Phase 2b Study Design Overview

Design

Open-label, repeat-dose study in 4 sequential ascending dosing cohorts
(up to 8 patients per cohort)

Population

Congenital HI ≥ 2 years old with continued hypoglycemia on SOC, by specified continuous glucose monitoring (CGM) and self-monitored BG (SMBG) thresholds

Duration

~26 weeks

- Screening – up to 5 weeks
- Treatment – 8 weeks
- Follow Up – 13 weeks

Assessments/ Endpoints

Primary: Time within range (70-180 mg/dL) by CGM
Secondary: duration/incidence of hypoglycemia by CGM/SMBG/fasting

Topline Results

Enable registrational Phase 3 planning and preparation for regulatory interactions

Dosing Cohort	Dose Levels and Bi-Weekly Dosing Regimen (mg/kg)			
	Week 1	Week 3	Week 5	Week 7
1	3	3	3	3
2	6	6	6	6
3	9	9	9	9
4	3	6	9	9

Topline results presented in 2Q 2022

Patient Demographics and Baseline Characteristics

Parameter	Cohort 1: 3 mg/kg (N=4)	Cohort 2: 6 mg/kg (N=8)	Cohort 3: 9 mg/kg (N=8)	Cohort 4: 3-9 mg/kg (N=3)	RZ358 Total (N=23)
Age (Mean, Range)	5.8 (2-12)	9.3 (2-22)	5.8 (2-17)	4.0 (2-6)	6.7 (2-22); N=16 ages 2-6
Gender (n, M / F)	4 / 0	5 / 3	3 / 5	1 / 2	13 / 10
Genetics (n, kATP / Other / Unknown)	1 / 0 / 3	5 / 1 / 2	4 / 1 / 3	1 / 1 / 1	11 / 3 / 9
CHI Rx (n, %)	4	7	6	3	20 (87%)
Diazoxide	2	3	1	2	8 (35%)
SSA (Long-acting/Short-Acting)	2 / 0	1 / 2	3 / 4	1 / 0	7 / 6 (56%)
Other (inc 2+ meds, pancreatectomy, enteral feeding)	0	2	6	1	9 (39%)
% Time Hypoglycemia (<70 mg/dL) by CGM (Mean, Range, PP Population)	16 (12-20; n=4)	22 (12-34; n=8)	26 (6-86; n=7)	29 (10-43)	23 (6-86; n=22)
Hypoglycemia Events / Wk by BGM (Mean, Range, PP Population)	10 (6-14; n=3)	19 (5-78; n=8)	17 (8-28; n=7)	8 (5-11; n=3)	16 (5-78; n=21)

- Patients enrolled on stable background therapies had:
  - Clinically-significant, and in many cases, substantial residual hypoglycemia indicating an unmet treatment need
  - Some hyperglycemia (>180 mg/dL) at baseline

RZ358 Was Generally Safe and Well Tolerated Across Doses

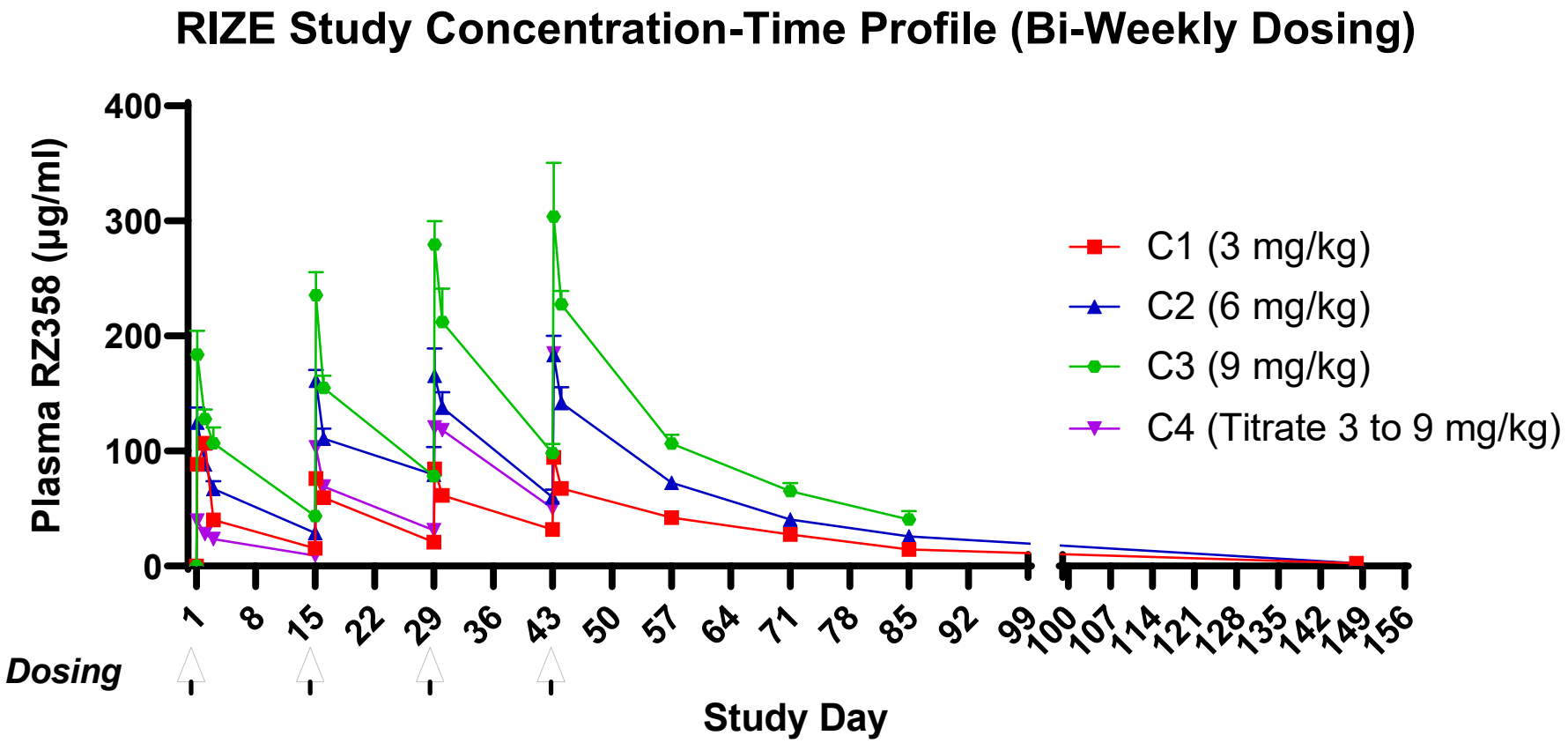
- No adverse drug reactions, AEs leading to study discontinuation, or dose-limiting toxicities
  - All 23 patients completed study in full (no discontinuations)
- In RZ358 treated subjects overall, 15 subjects (65%) experienced a total of 43 treatment-emergent AEs, compared to 10 subjects (43%) who experienced a total of 13 AEs outside of the defined treatment-emergent period (pre-treatment or >+42 days post-treatment)
  - No difference in time (or exposure)-adjusted AE rates
  - No dose-response
  - Generally mild and unrelated to study drug
  - No issues with GI tolerability
- Three patients experienced mild adverse events that were judged by Investigator(s) as related to study drug (hyperactivity, mild/transient infusion site rash, dizziness)
- Three patients experienced three unrelated SAEs (hospitalization), all deemed related to background conditions
- Mild hyperglycemia (>180 mg/dL) worsened from baseline in this patient group on SOC with some baseline hyperglycemia
- No increase from baseline in clinically relevant hyperglycemia (≥ 250 mg/dL) and no hyperglycemia AEs or adverse metabolic changes

Treatment Emergent Adverse Event Overview

	Non-TEAE (Pre/42d Post-Rx) (n=23)	RZ358 3 mg/kg (n=4)	RZ358 6 mg/kg (n=8)	RZ358 9 mg/kg (n=8)	RZ358 Titrate (n=3)	RZ358 Total TEAE (n=23)
Subjects with Adverse Events (AEs), n (%)	10 (43%)	2 (50%)	7 (87%)	4 (50%)	2 (50%)	15 (65%)
Total AEs	13	2	30[#]	7	4	43
Subjects with Serious AEs (SAEs), n (%)	0 (0%)	0 (0%)	2 (25%)	1 (13%)	0 (0%)	3 (13%)
Total SAEs	0	0	2	1	0	3
Subjects with PI-Judged Related AEs, n (%)	n/a	0 (0%)	2 (25%)	1 (13%)	0 (0%)	3 (13%)
Total Related AEs	n/a	0	3	1	0	4
Subjects with AEs by Severity, n (%)						
Grade 1	8 (35%)	2 (50%)	7 (87%)	2 (25%)	2 (50%)	13 (57%)
Grade 2	2 (9%)	0 (0%)	3 (38%)	1 (13%)	0 (0%)	4 (17%)
≥ Grade 3	1 (4%)	0 (0%)	2 (25%)	1 (13%)	0 (0%)	3 (13%)
Subjects Discontinued due to AEs, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

 # Majority of AEs in Cohort 2 were mild, judged unrelated to study drug, and experienced by 2 patients.

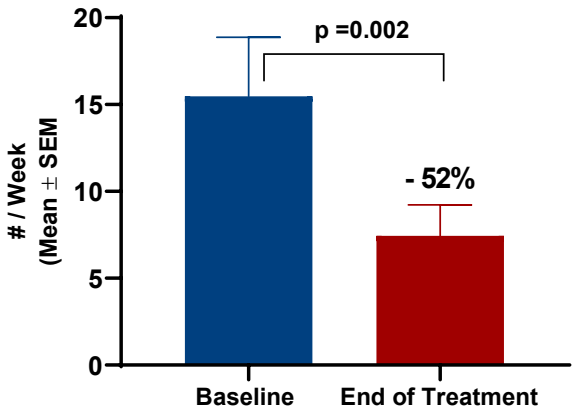
RIZE Study Pharmacokinetics: Dose-Dependent and Predictable Drug Concentrations



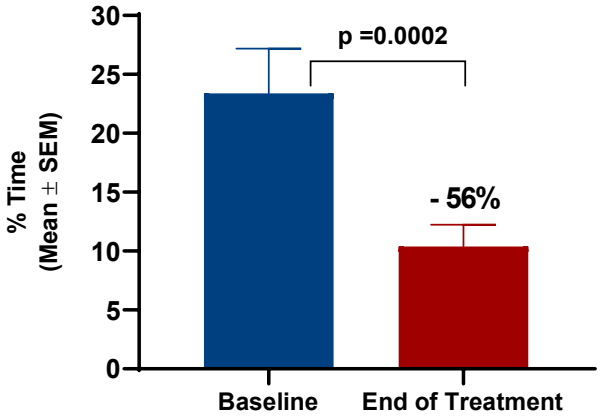
- Dependable concentrations independent of congenital HI patient factors (absorption, PO aversion, GI tolerability, etc)
- Half-Life > 2 weeks
- No apparent age dependencies
- Well below exposures in monkey toxicology studies (≥ 4-fold margin at highest dose)

Expectations of ≥ 25% Hypoglycemia Correction (Time and Events) Were Met and Exceeded Across Multiple Metrics

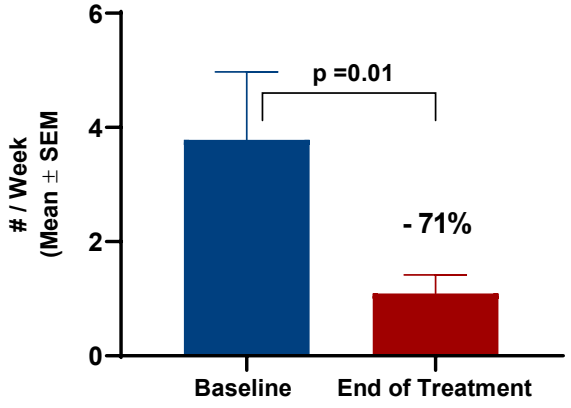
Hypoglycemia Event Rate by BGM
(Events Per Week <70 mg/dL) [N=21]



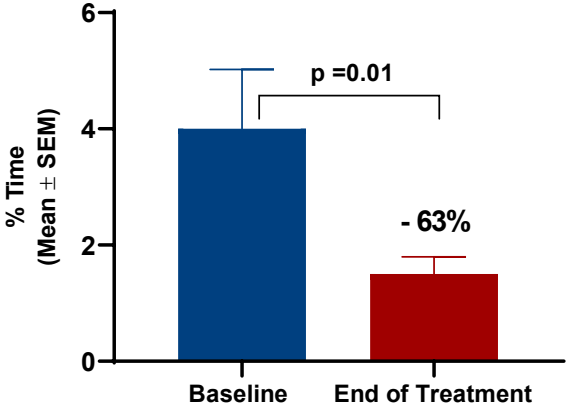
Hypoglycemia Duration by CGM
(Percent Time <70 mg/dL) [N=22]



Severe Hypoglycemia Event Rate by BGM
(Events Per Week <50 mg/dL) [N=21]



Severe Hypoglycemia Duration by CGM
(Percent Time <50 mg/dL) [N=22]



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Highly Significant Dose-Dependent Improvements in Hypoglycemia Events (BGM) and Time (CGM) Exceeded Study Expectations

Mean (Range)	RZ358 3 mg/kg (n=4) #	RZ358 6 mg/kg (n=8)	RZ358 9 mg/kg (n=7) ^	RZ358 Titrate (3-9 mg/kg) (n=3)	RZ358 Total Pooled (n=22)
Time in Hypoglycemia (<70 mg/dL) by CGM (%)					
Baseline	16.1	22.2	26.5	29.1	23.3 (6-86)
End of Treatment	10.5	9.2	9.4	15.8	10.4 (0.3-33)
% Change from BL (p-value)	***-35% (p=0.05)***	***-59% (p<0.01)***	***-65% (p=0.07)*** ^	***-46% (p=0.10)***	**-56% (p=0.0002)**
Time in Severe Hypoglycemia (<50 mg/dL) by CGM (%)					
Baseline	1.8	5.1	4.3	3.3	3.9 (0-21)
End of Treatment	1.3	1.4	1.7	1.6	1.5 (0-5)
% Change from BL (p-value)	***-25% (NS)***	***-73% (p<0.05)***	***-61% (NS)*** ^	***-52% (NS)***	**-63% (p=0.01)**
Hypoglycemia Events (<70 mg/dL) by BGM (events/week)					
Baseline	10.1	19.2	16.7	8.0	15.5 (4.5-77.8)
End of Treatment	7.8	9.9	5.3	5.3	7.5 (0-30.3)
% Change from BL (p-value)	***-22% (NS)***	***-48% (p=0.1)***	***- 68% (p<0.01)***	***-34% (p<0.05)***	***-52% (p=0.002)***
Severe Hypoglycemia Events (<50 mg/dL) by BGM (events/week)					
Baseline	1.6	5.5	4.2	0.5	3.8 (0.5-23.8)
End of Treatment	1.5	1.2	1.1	0.4	1.1 (0-5.5)
% Change from BL (p-value)	***-8% (NS)***	***-77% (p=0.1)***	***- 74% (p<0.05)***	***-20% (NS)***	***-71% (p=0.01)***

One patient at 3 mg/kg was excluded from the per protocol BGM analyses for failing to meet pre-specified minimum glucometer testing

^ One patient at 9 mg/kg was excluded from the per protocol CGM and BGM analyses for stopping background therapy while on study; Two 2 year-old patients in 9 mg/kg group wore CGM on the arm which may have impacted their results, but were included in analysis

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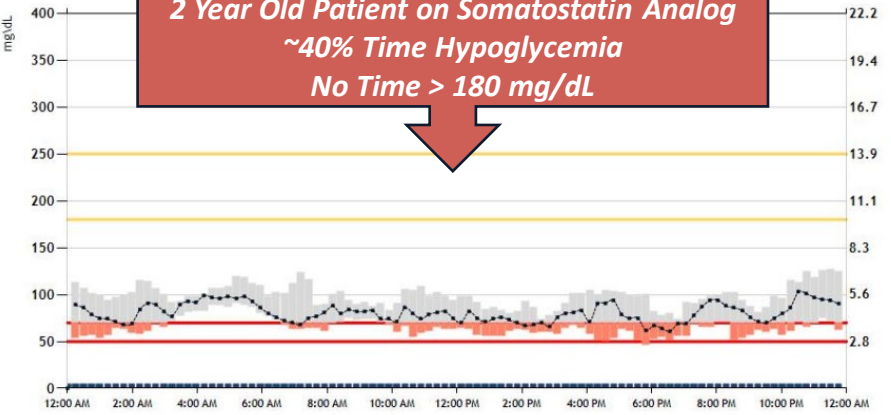
High Patient Response Rate at Clinically-Relevant Correction Thresholds

Responders N (%)	RZ358 3 mg/kg (n=4)	RZ358 6 mg/kg (n=8)	RZ358 9 mg/kg (n=7)	RZ358 Titrate 3-9 mg/kg (n=3)	RZ358 Total (n=22)
≥25% Correction of Hypoglycemia					
Severe (<50 mg/dL)	3 (75%)	7 (88%)	7 (100%)	2 (67%)	19 (86%)
Overall (<70 mg/dL)	3 (75%)	7 (88%)	7 (100%)	3 (100%)	20 (91%)
≥50% Correction of Hypoglycemia					
Severe (<50 mg/dL)	3 (75%)	6 (75%)	7 (100%)	2 (67%)	18 (82%)
Overall (<70 mg/dL)	1 (25%)	7 (88%)	7 (100%)	1 (33%)	16 (73%)
≥75% Correction of Hypoglycemia					
Severe (<50 mg/dL)	1 (25%)	5 (63%)	6 (86%)	2 (67%)	14 (64%)
Overall (<70 mg/dL)	1 (25%)	3 (38%)	5 (71%)	1 (33%)	10 (45%)

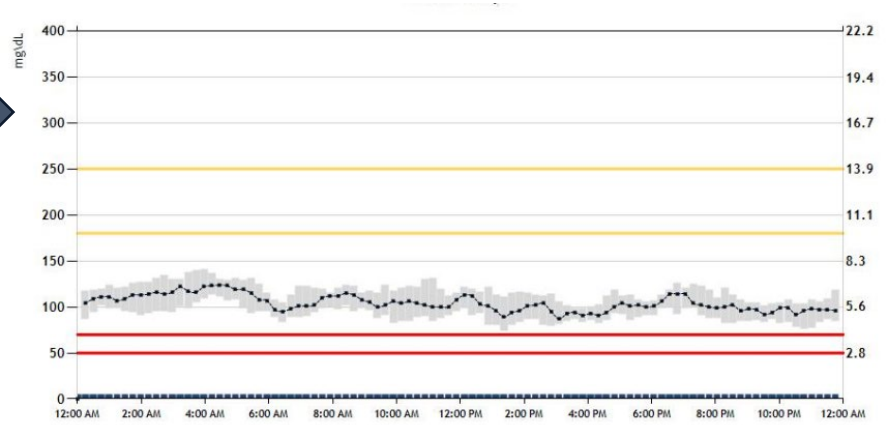
Potential for RZ358 to be an Effective Monotherapy Treatment

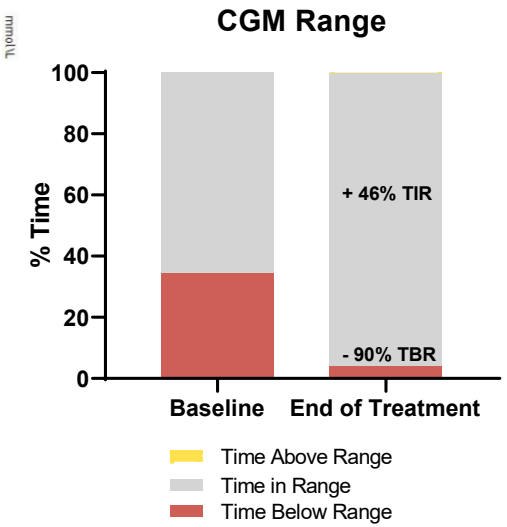
2 Year Old Patient on Somatostatin Analog
~40% Time Hypoglycemia
No Time > 180 mg/dL



+ RZ358
(6 mg/kg)

ABOVE HIGH THRESHOLD
75TH PERCENTILE
MEDIAN
25TH PERCENTILE
BELOW LOW THRESHOLD

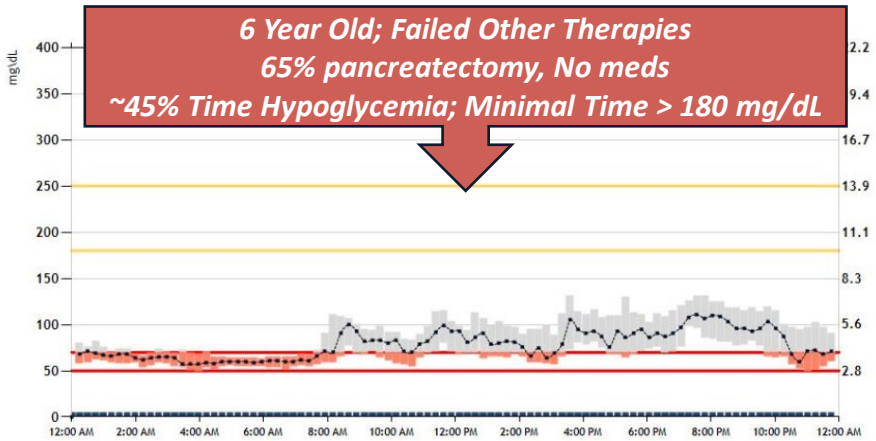




Baseline CGM period (≥ 10 days)

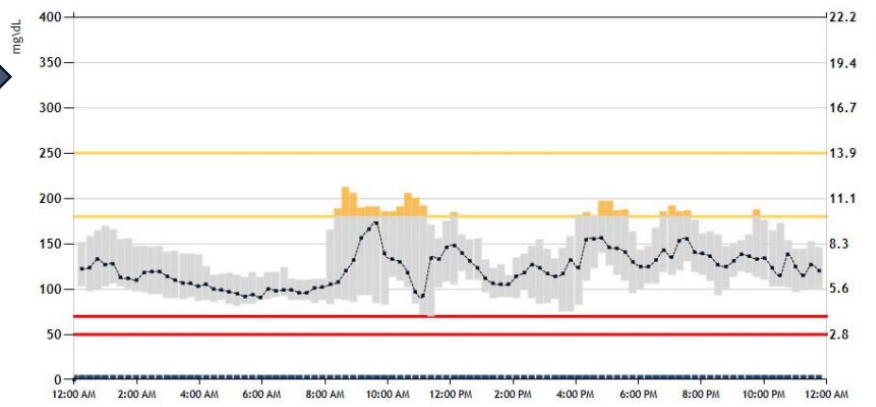
Treatment Evaluable CGM period (2-weeks)

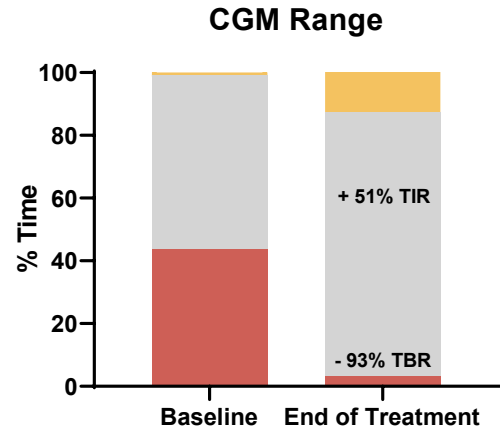
6 Year Old; Failed Other Therapies
65% pancreatectomy, No meds
~45% Time Hypoglycemia; Minimal Time > 180 mg/dL



+ RZ358
(9 mg/kg)

ABOVE HIGH THRESHOLD
75TH PERCENTILE
MEDIAN
25TH PERCENTILE
BELOW LOW THRESHOLD





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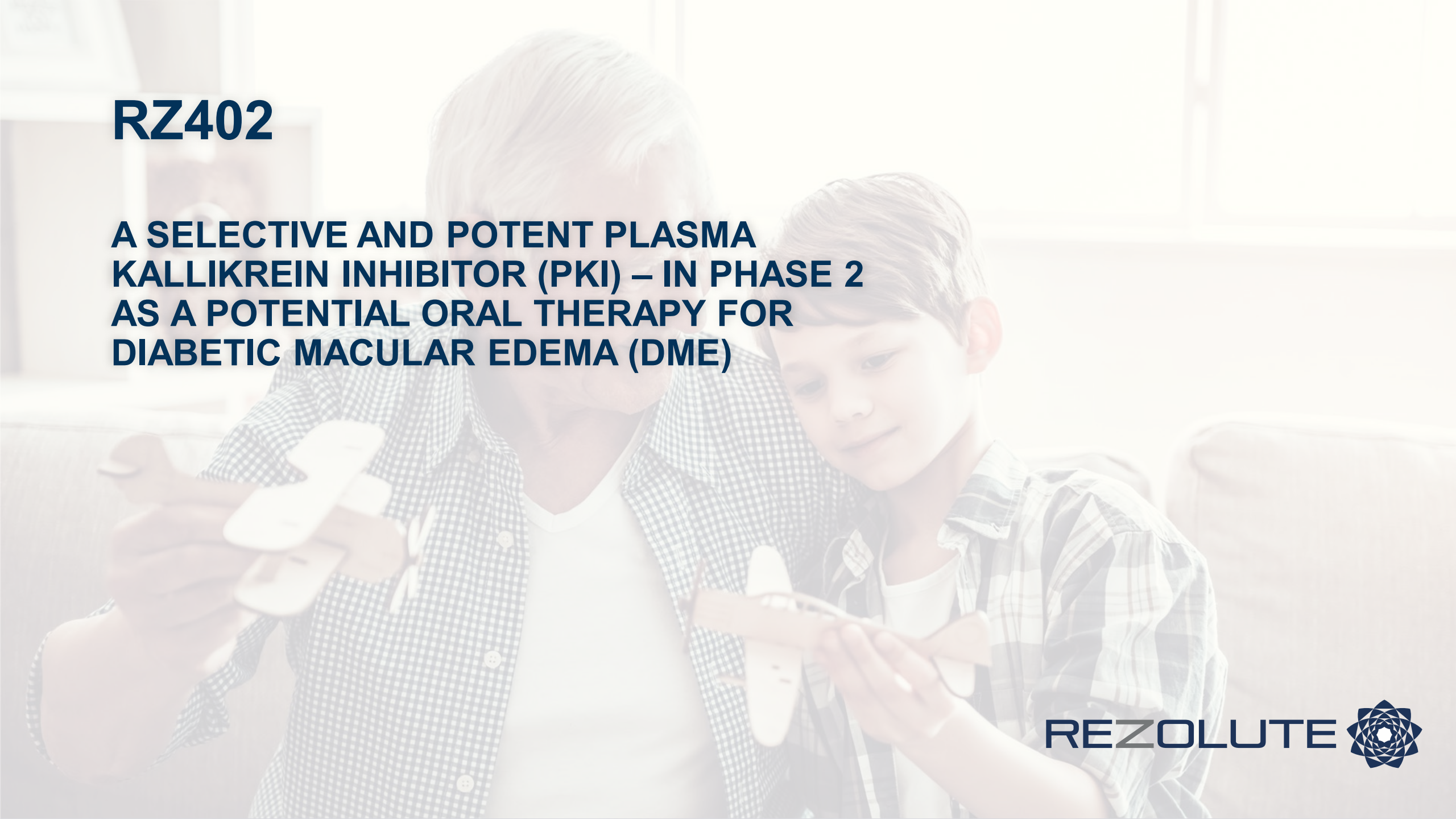
Summary of Results

- RZ358 was safe and effective in a diverse group of congenital HI patients (across age, gender, and genetics) who had continued hypoglycemia and some hyperglycemia on background SOC
- Improvements in hypoglycemia of ~75% at the mid (6 mg/kg) and top doses (9 mg/kg) and a high patient response rate
  - Improvements were comparable by both BGM (hypoglycemia events) and CGM (hypoglycemia time)
- Better than expected hypoglycemia correction resulted in mild, self-limiting, non-clinically meaningful hyperglycemia in patients taking background therapies
  - TIR (70-180 mg/dL) by CGM improved 8% across all doses, 16% at the top dose, and more significantly (>25%) in patients without baseline hyperglycemia on SOC
- Clear dose-response observed
- Results demonstrate the potential for RZ358 to be an effective combination or monotherapy for patients with congenital and syndromic HI

RZ402

A SELECTIVE AND POTENT PLASMA KALLIKREIN INHIBITOR (PKI) – IN PHASE 2 AS A POTENTIAL ORAL THERAPY FOR DIABETIC MACULAR EDEMA (DME)



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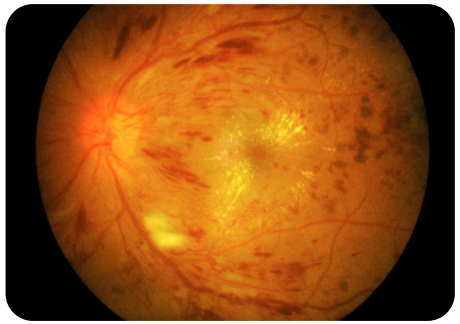
Diabetic Macular Edema (DME)

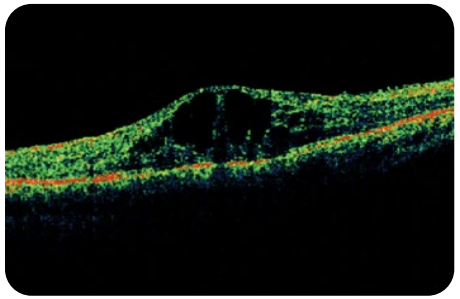
- DME is a microvascular complication of diabetes affecting the retinal blood vessels and a primary cause of blindness in the US
  - Chronic exposure to high blood sugar levels leads to loss of the blood-retinal-barrier resulting in leakage and fluid infiltration into the retina
  - Manifests as blind spots, floaters, blurry vision, and ultimately blindness

Increased Retinal Vascular Permeability



Leakage of fluid from vascular compartment into the retina

Macular Edema



Swelling of the central macula

Progressive Vision Loss and Blindness

10M have diabetic retinopathy[2] in US and 1-2M have DME[3,4]

1. CDC National Diabetes Statistics Report, 2020. 2. JAMA. 2010, 304(6):649-656. 3. JAMA Ophthalmology. 2014, 132(11):1334-1340. 4. Diabetes Care. 2012, 35(3):556-564.

Current SOC: Anti-VEGF Therapies Are Inadequate

- Anti-VEGF injections into the eye are the current standard of care (e.g., Lucentis and Eylea)
- Problematic route of administration
  - Initiation of therapy is delayed as disease progresses
  - Poor compliance with monthly injection regimen
  - Must be administered in clinical setting
  - Invasive injection and sub-optimal compliance limits potential market size
- Not effective in many patients as VEGF may not be implicated in all DME patients

1. Diabetes 2015, 64(10): 3588-3599 2. Ther Adv Endocrinol Metab. 2013, 4(6): 151–169

RZ402: Oral Therapeutic Product Candidate for DME

- Targets a different pathway, the Kallikrein–Kinin System (KKS), to address inflammation and vascular leakage
  - RZ402 potently inhibits kallikrein activation in human plasma
  - In dose dependent fashion, RZ402 potently suppresses vascular leakage (up to 80%) in relevant animal models
  - Possible treatment alternative for patients with a suboptimal response to anti-VEGF therapies
- Oral delivery provides for patient-controlled regimen and systemic exposure
  - Advantages in comfort and convenience – anticipated once daily capsule or tablet
  - Intended as monotherapy or combination with anti-VEGF injections
  - For prevention or treatment of DME
  - Continuous drug levels, targeting the vasculature, not the eye

Oral route of delivery may lead to earlier intervention, reach more patients and lead to better overall clinical outcomes

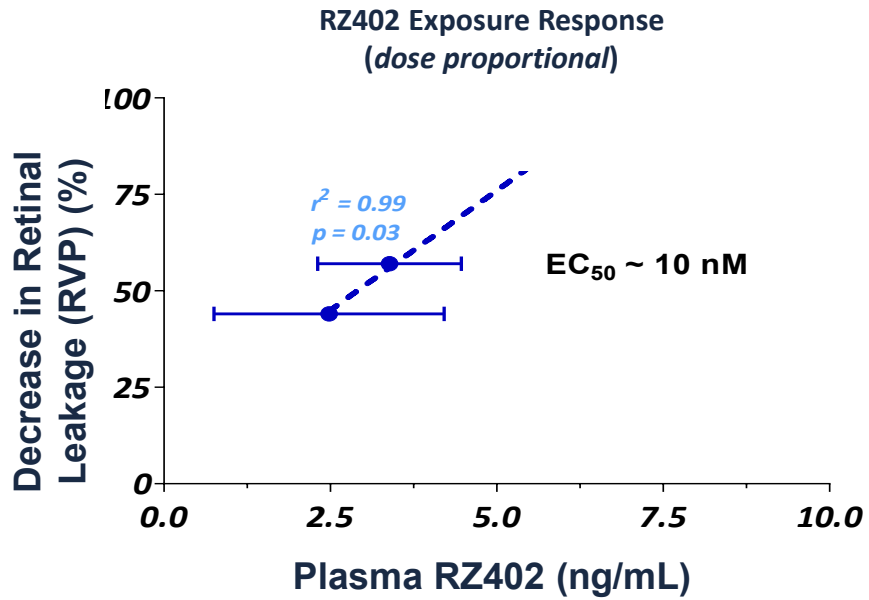
Disease Models Highlight RZ402 Efficacy

- Retinal vascular permeability (indicative of macular edema) was inhibited by RZ402 in rodent models of DME
- Low nanomolar potency was exhibited in rodent DME models

RZ402 Inhibits Retinal Vascular Permeability in Diabetic and Hypertensive Rodent Models

Animal Model	End Point	RZ402 Dose*	Inhibition
Diabetes	RVP	0.25 – 0.6 mg/kg/day	43-83%
Hypertension	RVP	0.2 – 0.4 mg/kg/day	60-92%
Diabetes	***Hematoma Expansion***	*0.4 mg/kg/day*	***85%***
Retinal Hemorrhage	***Retinal Leukostasis***	*1 mg/kg/day*	***>90%***

RZ402 is Highly Potent and Dose Proportional in Treating Vascular Permeability

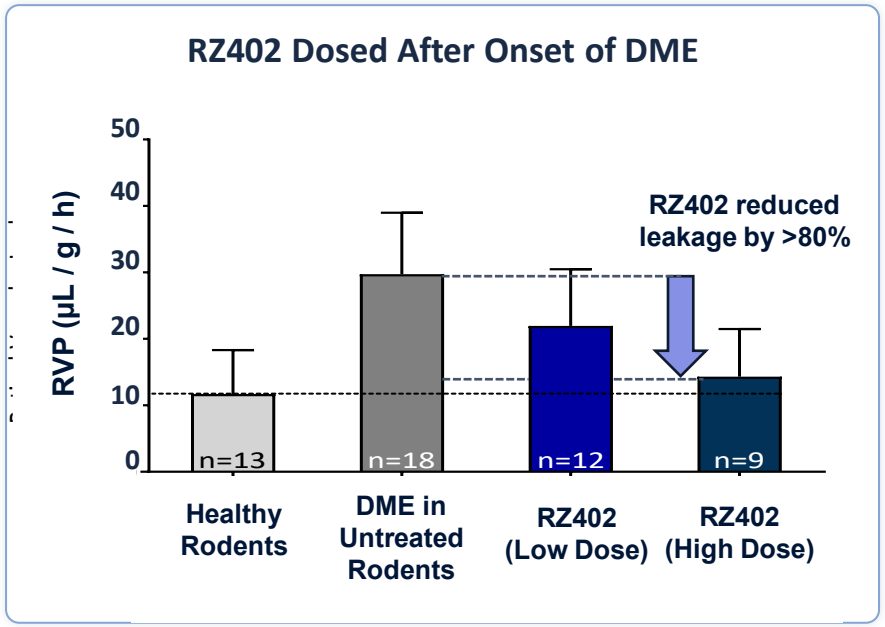


*Subcutaneous administration

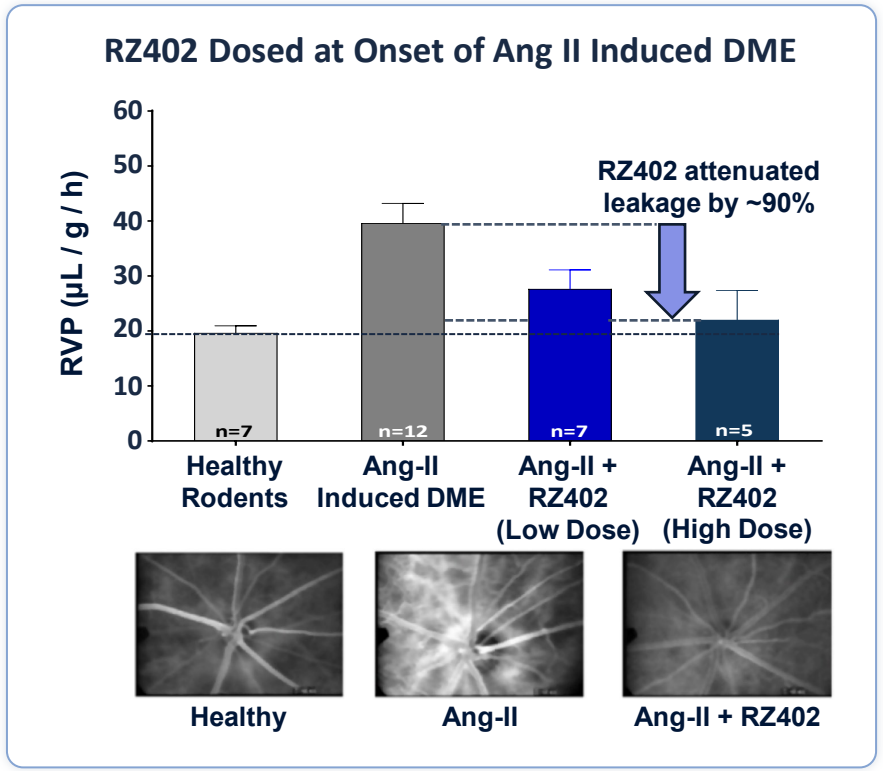
Systemic Delivery *Reversed* & *Prevented* Retinal Vascular Leakage

- Reversal of retinal vascular permeability (RVP) was seen when RZ402 was dosed in rodent DME models
- Angiography studies in a rodent DME model highlighted that RZ402 may prevent Angiotensin II induced RVP

RZ402 reversed vascular leakage by >80%



RZ402 prevented vascular leakage by ~90%



Hypertension 2009, 53:175-181; Diabetes. 2011 May; 60(5): 1590–1598

RZ402: Phase 1 (SAD and MAD) Study Results Support Once Daily Oral Dosing

Design/Dosing

Single center, randomized, double-blind, placebo-controlled study in 3 sequential dosing cohorts in the SAD study (25, 100, 250 mg) and an additional 4th cohort (500 mg) in the MAD study administered once-daily

Population

Each cohort comprised of 10 healthy volunteers randomized 8:2 active vs placebo, for a total of 30 participants in the SAD study and 40 participants in the MAD study

Primary Objectives

Assess the safety and tolerability of once-daily oral administration of RZ402 and determine the PK profile; achieve steady-state target concentrations

Exploratory Objectives

Investigate effects of repeat doses of RZ402 on biomarkers of target engagement (plasma kallikrein inhibition) and related PD effects

Timeline

SAD study concluded in 2Q 2021

MAD study concluded in 1Q 2022

Phase 2 proof-of-concept study planned for 4Q 2022

- The Phase 1 program met its primary safety and pharmacokinetic endpoints and enables the Phase 2 proof-of-concept study:
  - RZ402 was safe and well tolerated across all doses, without dose-limiting toxicities
  - RZ402 was adequately bioavailable with dose-dependent increases in systemic exposures
  - Repeat-dosing to steady-state resulted in the highest concentrations of RZ402 explored to date
  - Results at both peak and 24-hour trough substantially exceeded target concentrations based on a combination of in-vitro and in-vivo profiling

MAD Study Results: Safety

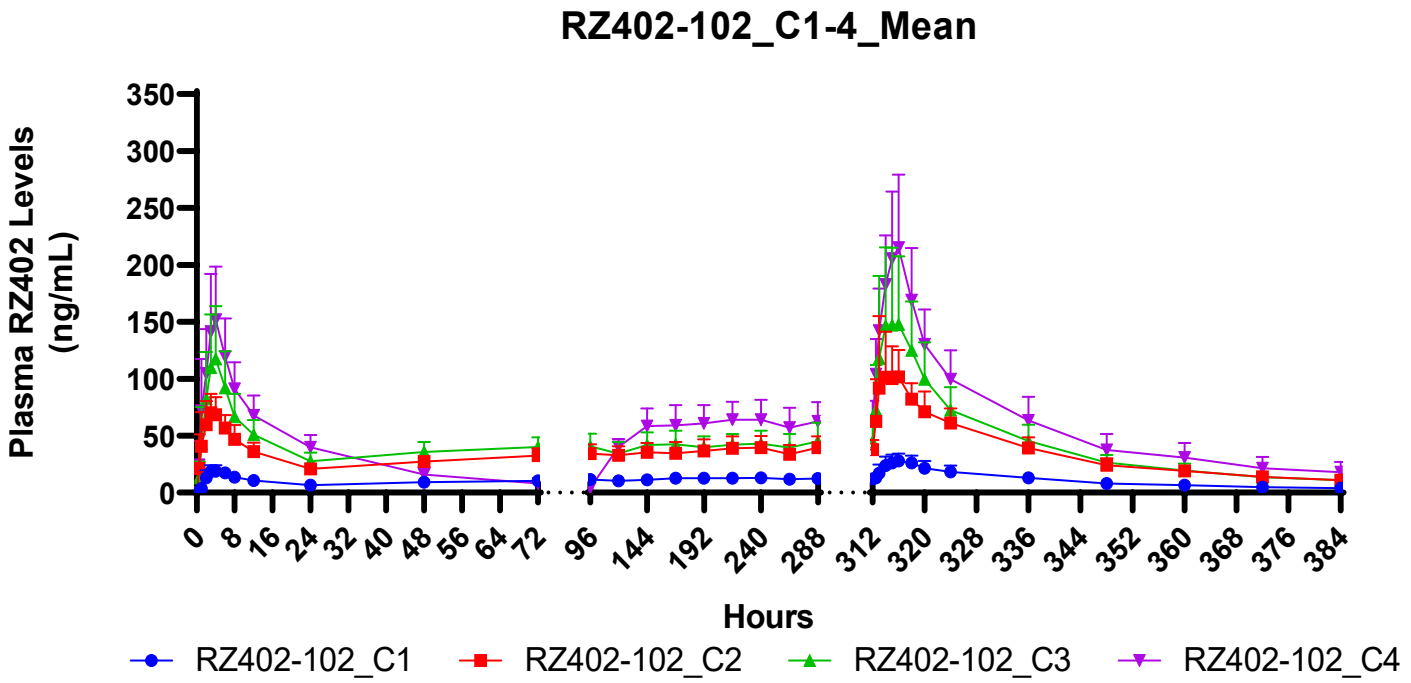
- No adverse drug reactions, serious adverse events, or study discontinuations
- 19 subjects (59%) in treatment group had a total of 48 AEs compared to 5 subjects (63%; 15 AEs) in placebo group
- Some GI events were reported but they were mild and not dose-dependent, so relationship to study drug is unclear
- No effect on blood pressure or heart rate
- Comprehensive safety eye exams were unremarkable
- Laboratory evaluations unremarkable (including coagulation studies)

	RZ402 25-mg (N = 8)	RZ402 100-mg (N = 8)	RZ402 250-mg (N = 8)	RZ402 500-mg (N = 8)	Placebo (N = 8)	Combined RZ402 (N = 32)	Overall (N = 40)
Subjects with at least 1 TEAE, n (%)	6 (75.0)	5 (62.5)	3 (37.5)	5 (62.5)	5 (62.5)	19 (59.4)	24 (60.0)
Subjects with a related TEAE, n (%)	4 (50.0)	2 (25.0)	1 (12.5)	4 (50.0)	2 (25.0)	11 (34.4)	13 (32.5)
Subjects with a grade 3 or greater TEAE, n (%)	0	0	0	0	0	0	0
Subjects with a serious TEAE, n (%)	0	0	0	0	0	0	0
Subjects with a related serious TEAE, n (%)	0	0	0	0	0	0	0
Subjects with a TEAE leading to study discontinuation, n (%)	0	0	0	0	0	0	0
Subjects with a related TEAE leading to study discontinuation, n (%)	0	0	0	0	0	0	0
Number of TEAEs	24	8	6	10	15	48	63
Number of related TEAEs	10	2	3	6	5	21	26
Number of grade 3 or greater TEAEs	0	0	0	0	0	0	0
Number of serious TEAEs	0	0	0	0	0	0	0
Number of related serious TEAEs	0	0	0	0	0	0	0
Number of TEAEs leading to study discontinuation	0	0	0	0	0	0	0
Number of related TEAEs leading to study discontinuation	0	0	0	0	0	0	0

RZ402 was generally safe and well-tolerated

MAD Study Results: Single and Repeat Dose Pharmacokinetics

- Dose-dependent increase in systemic exposures
- Highest concentrations explored to date
- Drug accumulation following repeat dosing ≤ 2-fold
- 24-hour levels and half-life of ~20h support potential for once daily oral dosing
- Good safety profile observed in the clinic, and large safety margins to animal toxicology doses and exposures



Cohort 4 dosing schedule: D1-D4: Single dose on day 1; D5-14: Repeat QD dosing

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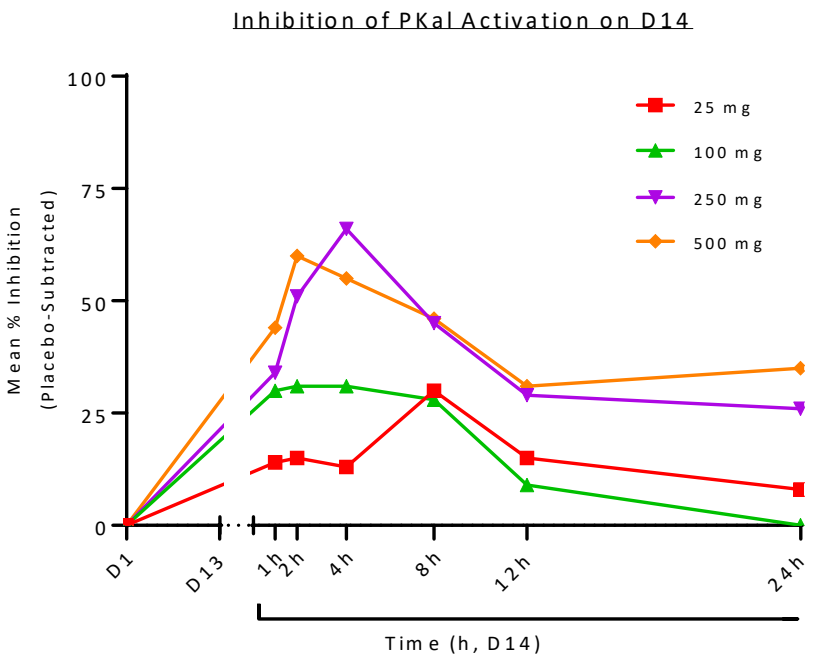
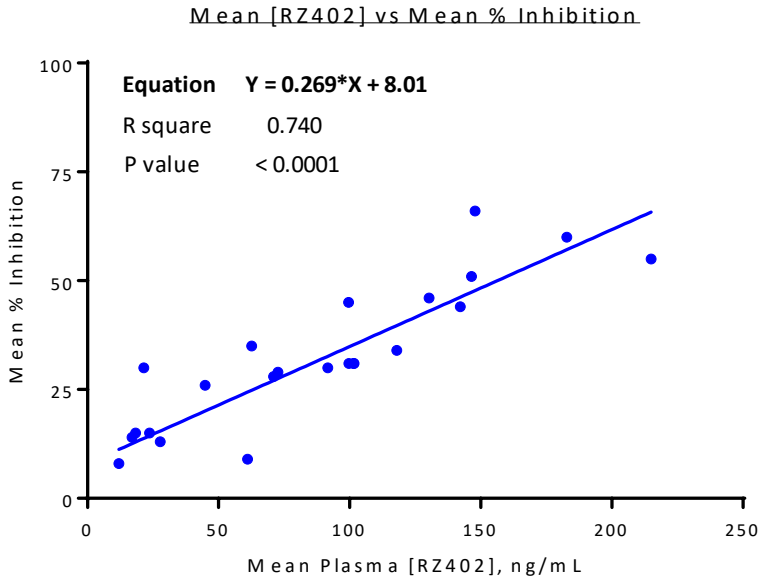
MAD Pharmacodynamic Results: Dose-Dependent Plasma Kallikrein Inhibition



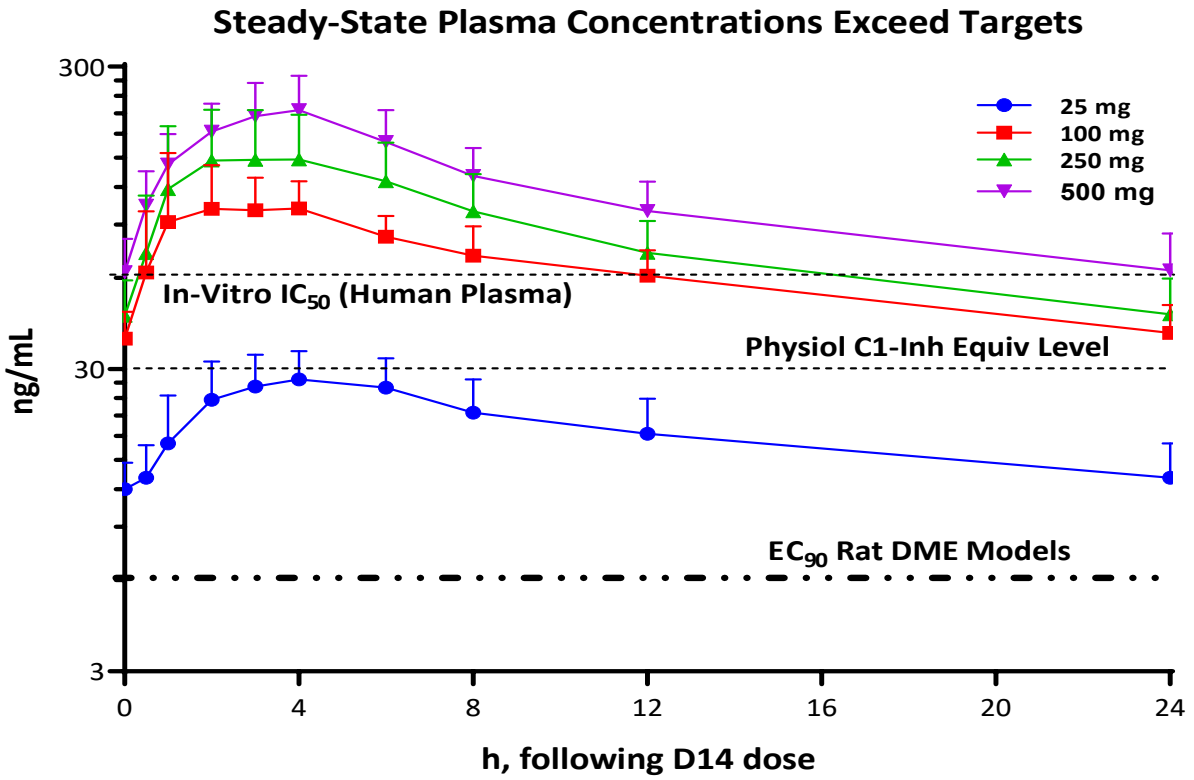


*Based on Plasma Kallikrein Activity in Human MAD Plasma Samples Using Ellagic-Acid Activation Assay

MAD Study Results: Pharmacologic Target Concentrations Achieved with Once Daily Oral Dosing

- Target concentrations achieved at the lowest dose administered and between daily doses (trough levels)
  - Daily dosing with RZ402 inhibited plasma kallikrein in a dose and concentration-dependent manner throughout the 24-hour dosing interval

- Potent *in-vivo* efficacy has been established with RZ402 in several animal models
  - ***In-vivo*** EC_{50-90}: 3-7 ng/mL (C_{ss})
  - RZ402 may localize at the blood vessel site of action to exert greater pharmacologic effects
  - Highly potent in-vivo effects may predict higher translatability into the clinic, with better efficacy than current oral therapies



Phase 2 POC

RZ402-201 Study Overview

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RZ402-201 Study Design Overview

Design

- Multi-Center, Randomized, Double-Masked, Placebo-Controlled Parallel-Arm Study
- Total of ~100 subjects, with up to 25 in each arm at ~25 sites in the US

Dosing

- Three active arms (50mg, 200mg, 400mg) compared to the Placebo arm
- Once daily oral administration for 3 months
- Selected doses projected to exceed target concentrations

Target Patient Population

- DME with mild to moderate NPDR
- CST of ≥320 µm (or corresponding values)
- BCVA of ≤78 ETDRS letters (≤20/25 on Snellen chart)
- Treatment naïve or no more than 3 anti-VEGF injections previously

Primary Endpoints

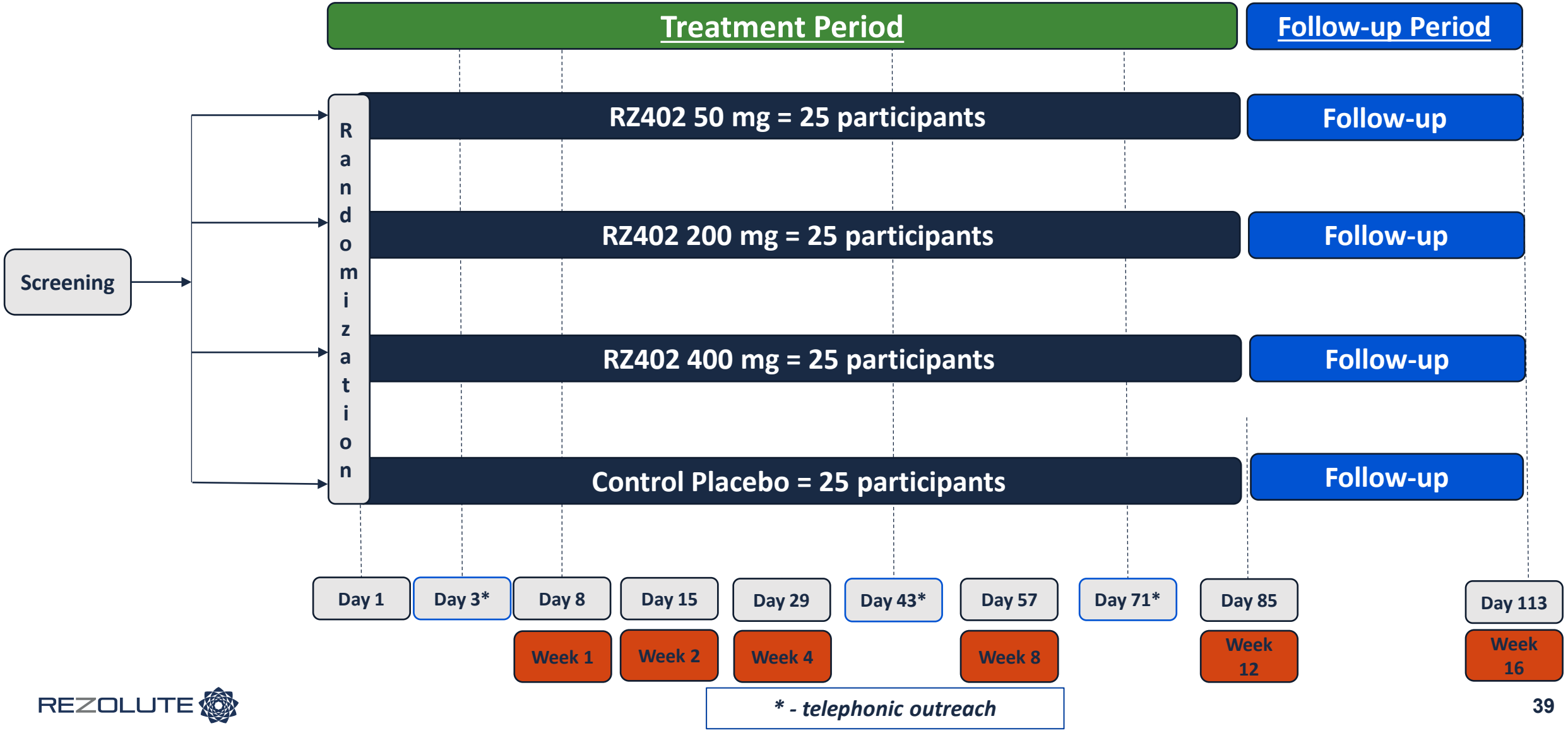
- Safety
- Efficacy (change in CST from baseline)

Secondary Endpoints

- Change in BCVA from baseline
- Change in DRSS score
- Repeat dose Pharmacokinetics in Patient Population

Proof of concept study topline data expected by 1Q 2024

RZ402-201 Study Design



Milestones

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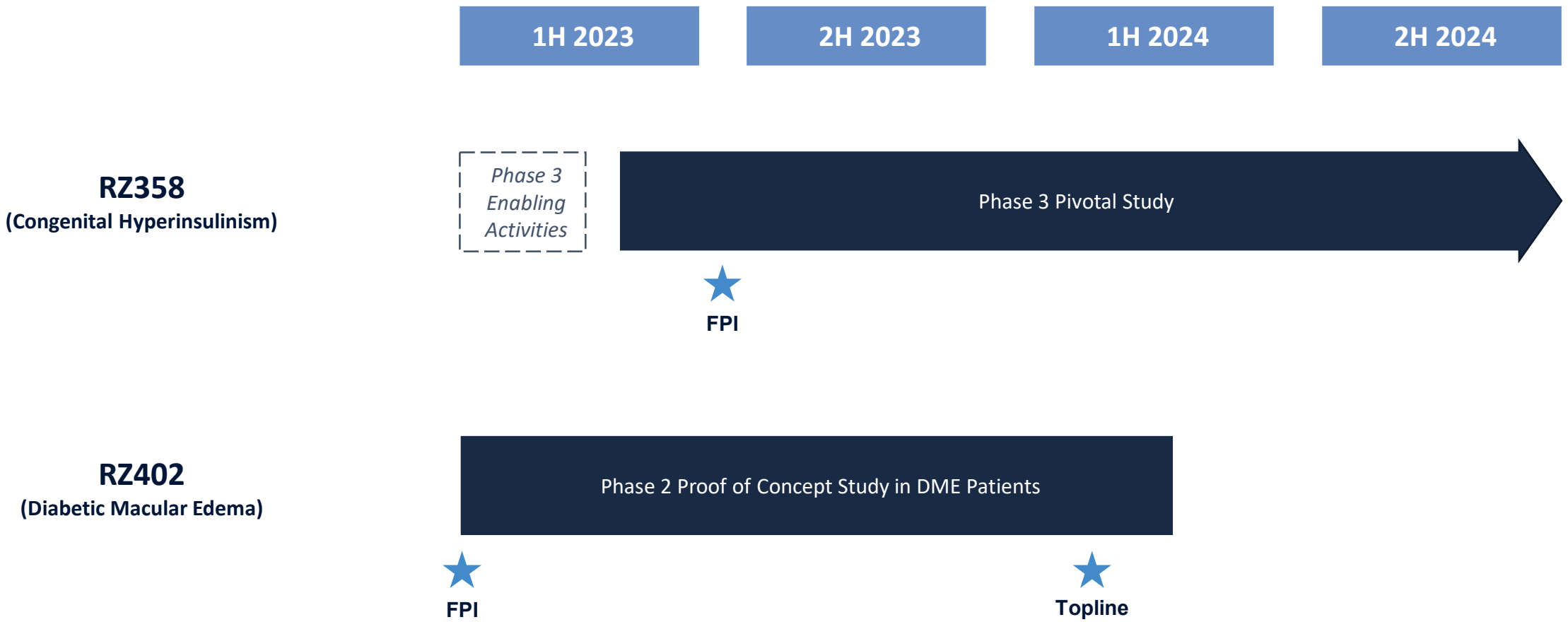
Near-Term Catalysts



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Thank you

December 2022