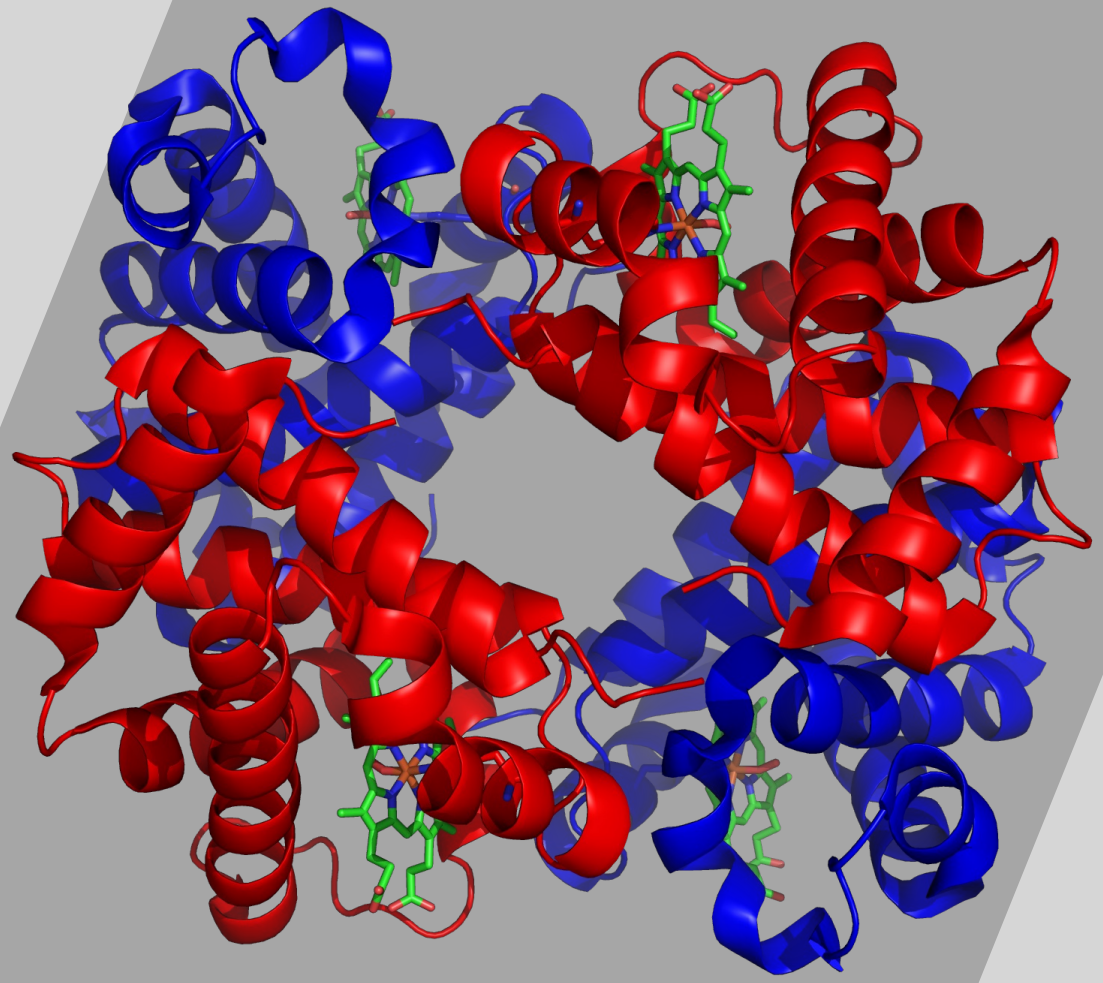
HbS Polymerization Inhibitors for Sickle Cell Disease

Treating the Whole Disease to Eliminate Hemolysis and Vaso-Occlusion



ILLEXCOR THERAPEUTICS

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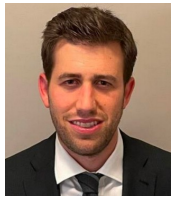
Executive Summary

- About 160,000 individuals in the US and EU and greater than 10 million globally affected by **sickle cell disease**
- A **disease modifying** oral drug would be the holy grail for treating most patients in the US and worldwide
  - **Problem -** drug candidates to date have only modest clinical benefits with severe residual disease sequalae
  - Persistent anemia and vaso-occlusive crises (VOCs) are both predictors of poor long-term prognosis
- Our lead drug **ILX002** is a Direct Hemoglobin S Polymerization Inhibitor for sickle cell disease
  - First and only drug that directly blocks polymerization by disrupting interactions between HbS molecules
  - ILX002 virtually eliminated residual hemolysis and restored normal Hb levels in humanized SCD mice
- Strong management team with decades of experience in pre-clinical and clinical development at big pharma
- IND program to be completed in mid-2025 with first-in-human Phase I/IIa clinical trial to follow immediately
- Potential for exit through IPO or strategic sale after End of Phase II meeting in less than 2 years

Executive Management Team



Andrew N. Fleischman, MD – Founder, Chief Executive Officer

- Physician-scientist with expertise in discovering and developing promising biotechnologies
- Dedicated company builder - founded multiple successful companies and raised > $25M in 3 years
- Broad expertise in discovery, development, clinical translation, IP, regulatory and business strategy

R. Clark Brown, MD – Chief Medical Officer

- Widely recognized clinical leader who has led development of multiple early and late-phase drugs for SCD (Oxbryta, GBT601, Etavopivat, crizanlizumab, and rivipansel)
- Most recently global clinical lead at Pfizer for Oxbryta and early phase development of GBT601

Martin K. Safo, PhD – Founder, Chief Scientific Officer

- World renowned expert on hemoglobin modifying drugs and SCD
- Over 30 years of experience in drug discovery with multiple drugs reaching the clinical stage, including RSR13 and Aes-103

David R. Light, PhD – VP of Research & Development

- Senior PI with 4 decades of industry experience with Sanofi, Biogen, Bayer, Genentech, & others
- Led pre-clinical teams for many INDs and several NDAs (Eloctate, Alprolix, Enjaymo)
- Subject matter expert in hematology and rare disease

Yash Shenoy, MBBS, MBA – Head of Business Development

- Seasoned BD professional - closed over $500M in licensing and partnership deals
- Previously BD role at publicly traded oncology company Apollomics.
- Also led growth capital investments (>$100M) in life science sector for InvAscent

CLEU DIAGNOSTICS
AMPEDRNA BIOSCIENCES
GBT
Pfizer
VCU
AesRx
SANOFI
Biogen
Bioverativ
apollomics

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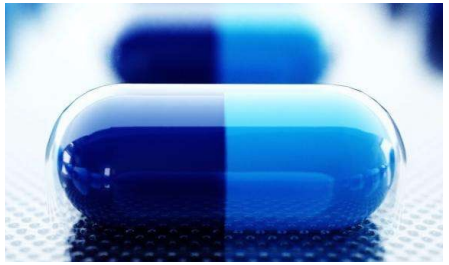
Target Market

- One of the most common rare diseases globally
  - 300,000 babies born annually with SCD
  - 160,000 individuals in the US and EU, and up to 10 million people worldwide
- Total addressable market greater than $40 billion per year worldwide
- Disproportionately affects underserved populations with significant unmet need
- Consequently, huge interest in this important scientific focus area from pharma

Competitive Landscape

- Bone marrow transplant since 1980s and more recently *ex vivo* gene therapy offer a potential cure for SCD
  - Ex vivo gene therapy is a form of autologous HSC transplant with genetic modification outside of the body
  - Substantial morbidity and risk due to myeloablative conditioning (e.g., infertility, predisposes to cancer)
  - Insurance companies must bear large upfront cost (Casgevy $2.2M, Lyfgenia $3.1M)
  - Only for minority of patients with most severe disease - Est. 200 to 800 patients to be treated annually by 2030
- Disease modifying oral therapy remains the **holy grail for most patients**
  - With recent withdrawal of Voxelotor, no FDA approved oral drug for sickle cell disease since 1990s
  - Drug candidates to date have only modest clinical benefits that do not adequately address unmet need
    - No drug provides disease-modifying benefits tantamount to a functional cure

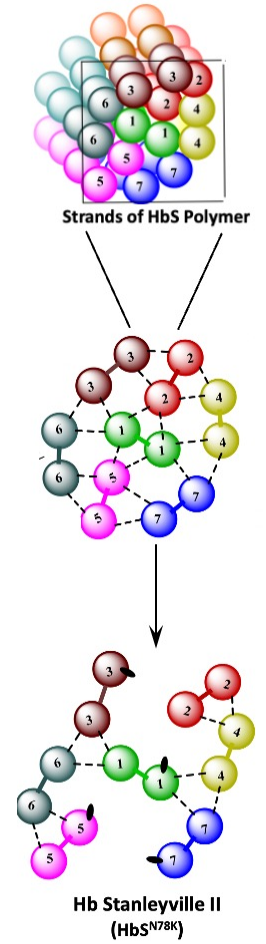


Genetic Basis for New Class of Polymerization Inhibitors

What we know from rare natural co-inherited hemoglobin point mutations in SCD

- Sickle mutation in β-globin ($\beta 6^{Glu \rightarrow Val}$) results in polymerization of deoxygenated HbS
- Hb Stanleyville II ($\beta 6^{Glu \rightarrow Val}/\alpha 78^{Asn \rightarrow Lys}$) is rare double mutant HbS variant in Congo & Sudan
  - $\alpha 78^{Asn \rightarrow Lys}$ mutation on α-globin alters the surface of the αF-helix to block HbS polymerization
  - Interrupts intermolecular interaction between helical double filaments within HbS fibers
  - Individuals with Hb Stanleyville II have **no signs of hemolytic anemia or VOCs**

ILX002 is first in a new class of HbS Polymerization Inhibitors that directly interfere with intermolecular interactions of HbS by mimicking Hb Stanleyville II



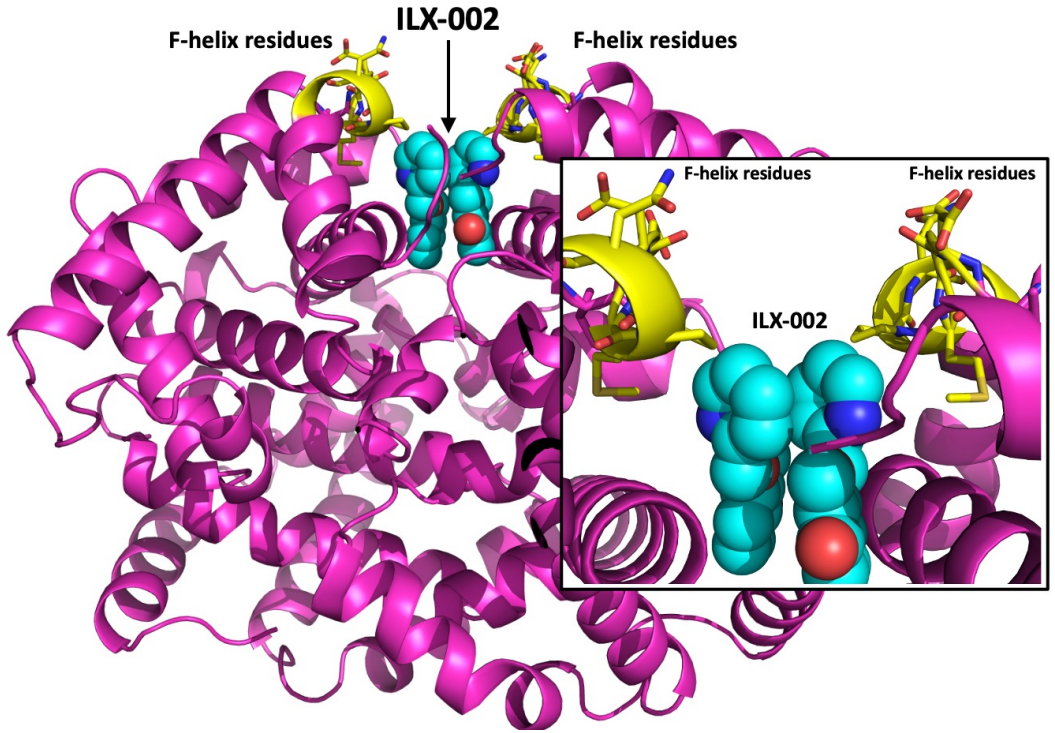
Rhoda MD, et al. *Biochem Biophys Res Commun*. 1983; 111(1):8-13.

Watowich SJ, et al. *J. Mol. Biol.* 1989; 209:821-828.

Burchall G and Maxwell E.. *Pathology*. 2010; 42(3):310-312.

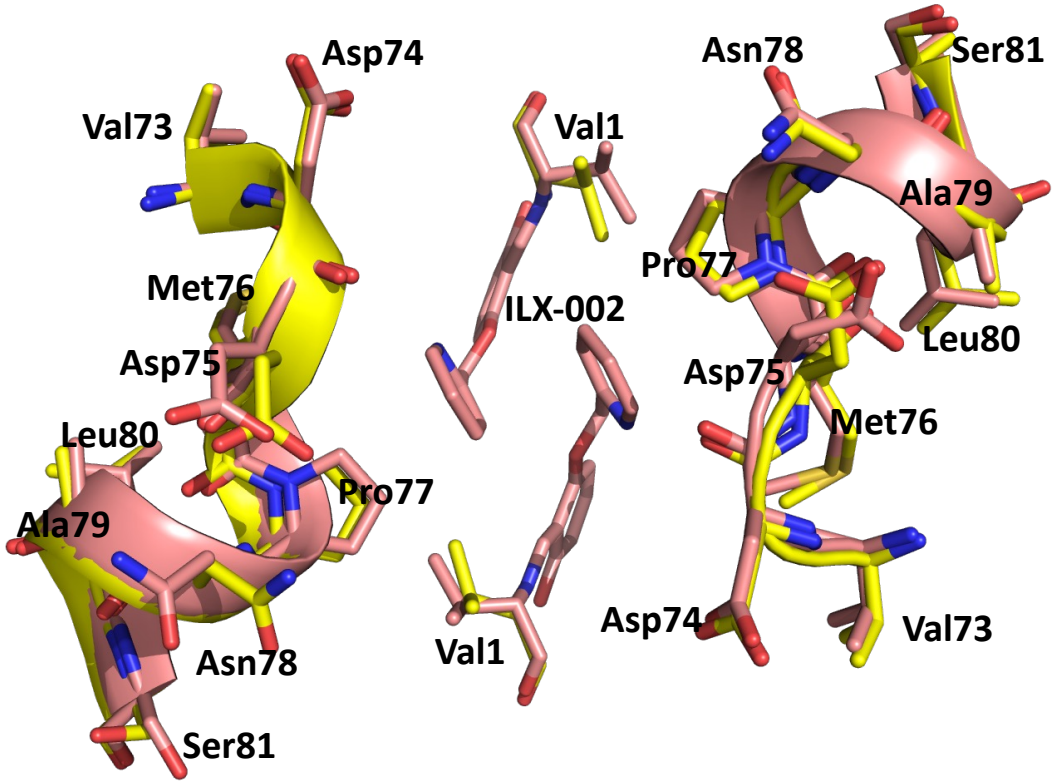
How It Works

- ILX002 is the first and only drug that binds to Hemoglobin S and directly blocks polymerization
- ILX002 makes **direct interactions** with residues on the surface of the αF-helix to **fundamentally disrupt** key intermolecular contacts between HbS molecules
- Mimics biophysical effect of Hb Stanleyville II, which does not polymerize



Crystal structure of ILX002 bound to HbS

ILX002 Mimics Effects of Hb Stanleyville II

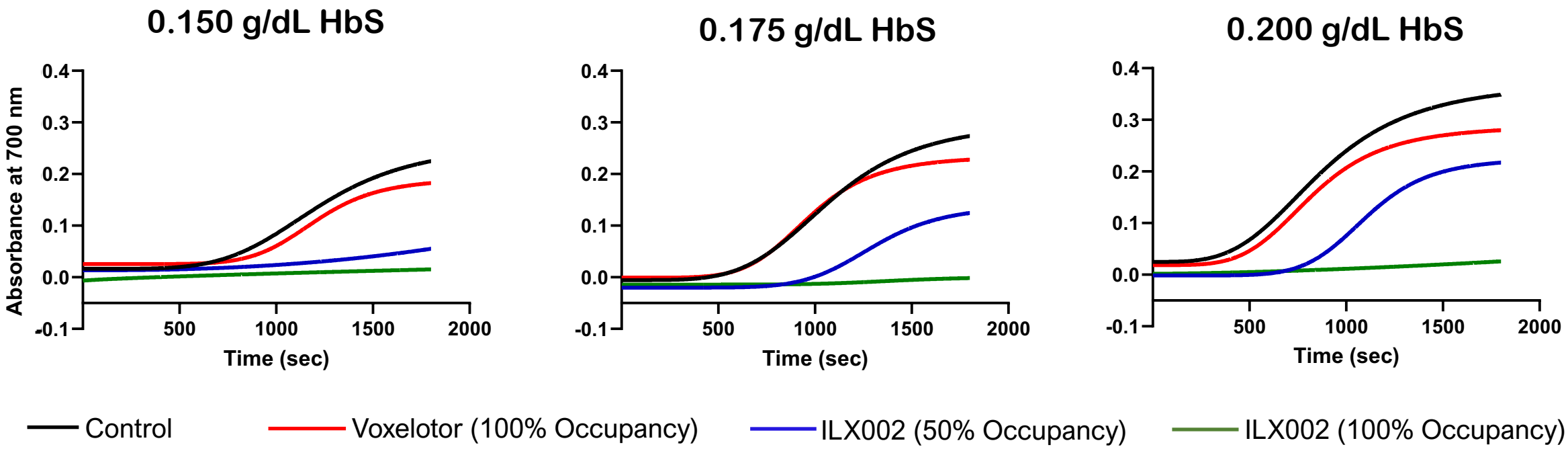


Superimposed crystal structures of αF-helix residues for native HbS (yellow) and HbS-ILX002 complex (pink)

Residue	Backbone Carbon (Cα)	Side-chain
Val73	0.39 Å	0.42 - 0.60 Å
Asp74	0.41 Å	0.45 - 0.76 Å
Asp75	0.57 Å	0.93 - 1.07 Å
Met76	0.50 Å	0.48 - 0.84 Å
Pro77	0.85 Å	0.77 - 1.00 Å
Asn78	0.55 Å	0.44 - 3.67 Å
Ala79	0.55 Å	0.56 Å
Leu80	0.67 Å	0.83 - 0.98 Å
Ser81	0.76 Å	0.74 - 2.7 Å
Ala82	0.87 Å	0.87 Å

- Binding of ILX002 to HbS causes a dramatic shift of backbone and side chain residues of the αF-helix and EF corner
  - Similar to Hb Stanleyville II ($\alpha 78^{Asn \rightarrow Lys}$), Asn78 is notably displaced by nearly 4 angstroms with a complete shift in its orientation

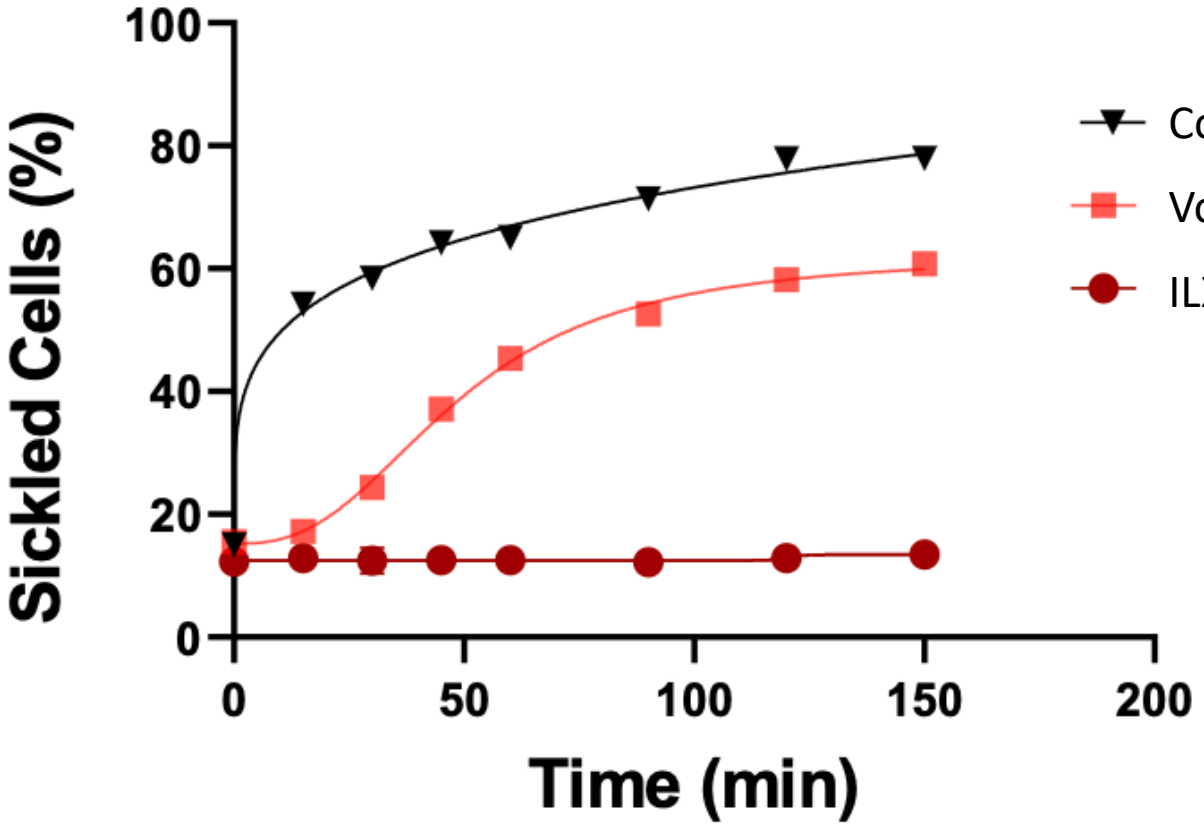
ILX002 Profoundly Increases Polymerization Delay Time

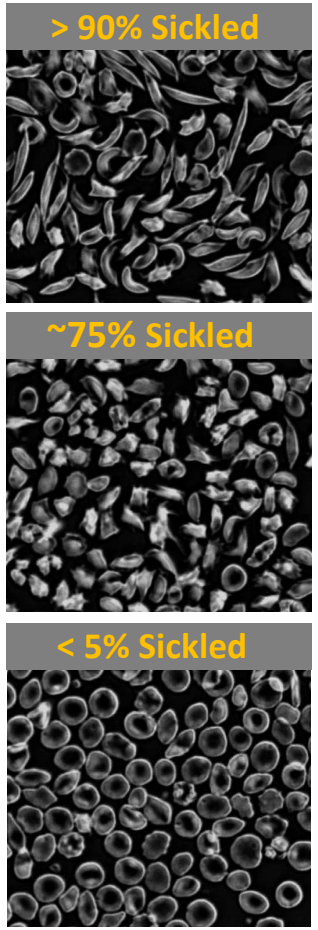


- Classic polymerization delay time assay conducted with chemical deoxygenation of free Hemoglobin S
- ILX002 exhibits unprecedented activity as the first small molecule drug to directly increase polymerization delay time
- Profound delay with ILX002 is similar in magnitude to well-characterized protective phenotypes (e.g., 30% HbF or SC trait)
  - Correspondingly, potential to achieve benign phenotype with resolution of symptoms and sequalae

Method as described in Zhenning and Russell. *Analytical Biochemistry*. 2002; 306(2):349-352.

O_2-Independent Inhibition of RBC Sickling

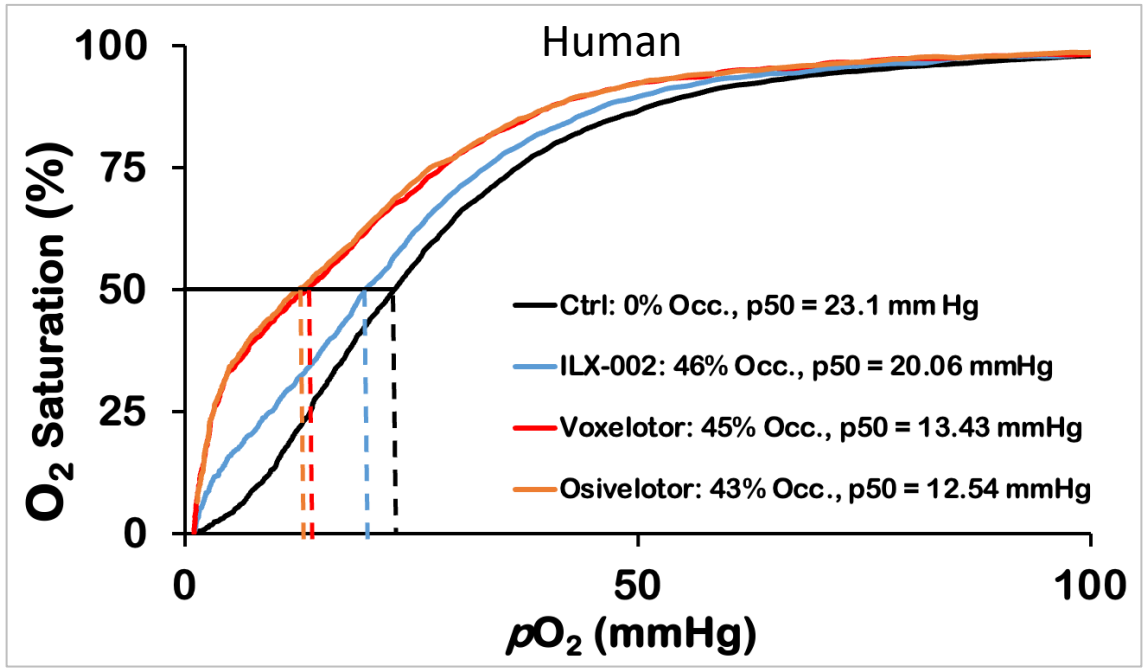




- *Ex vivo* study with whole blood from human SS donors incubated with N_2 gas (anoxic conditions)
- Highly potent and sustained inhibition of RBC sickling with ILX002 for greater than 2 hours in anoxia
- ILX002 inhibits sickling throughout **entire circulation**, even areas with low O_2 tension (e.g., bone, renal medulla)

Method as described in Abdulmalik O et al. *Sci Rep*. 2020; 10:20277.

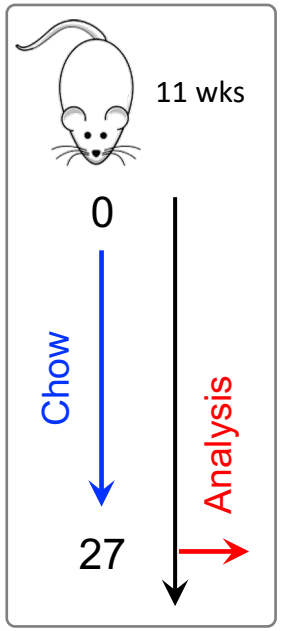
Minimal Impact on O_2 Dissociation



Osivelotor = GBT601

- ILX002 preserves normal physiology of O_2 dissociation in highly therapeutic range (Hb $\geq$12 g/dL with p50 in normal range)
- Conversely, Voxelotor and Osivelotor severely alter O_2 dissociation (p50 < 15 mmHg) to achieve meaningful efficacy
- Dramatic shift in O_2 affinity for meaningful clinical response with Voxelotor and Osivelotor results in loss of cooperativity
  - Natural high affinity hemoglobins (e.g., HbF, Hb Chesapeake) - p50 rarely less than 20 mmHg
  - Profound extramedullary erythropoiesis (Hb >18 g/dL) with p50s < 15-20 mmHg - unclear safety for SCD patients

Transformative Efficacy in Townes SCD Mice

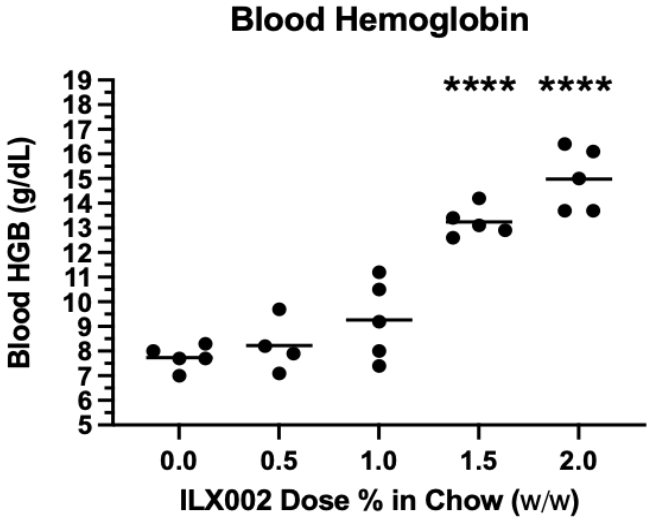


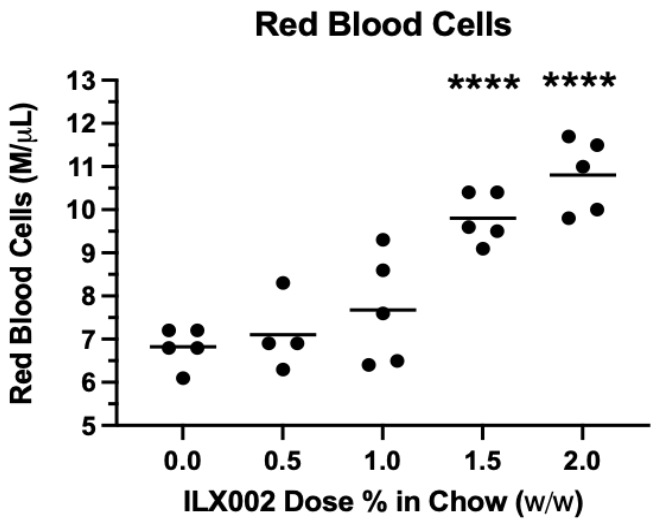
Humanized SS mice, n=5

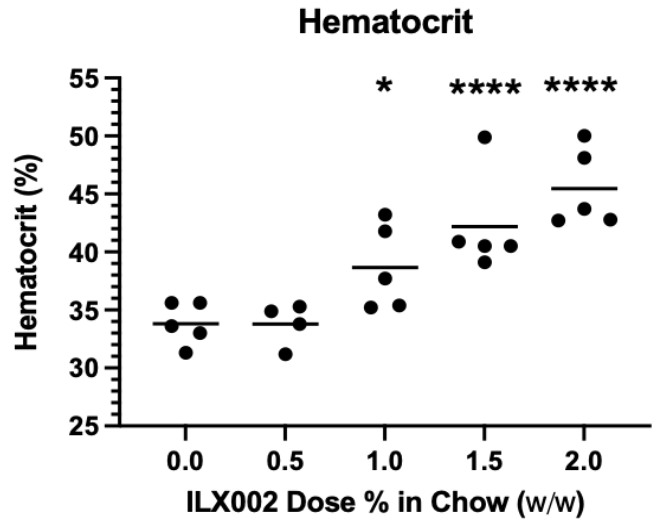
Mean	Vehicle	0.5% Chow	1% Chow	1.5% Chow	2% Chow
Hb Occupancy (%)	0	11	24	44	56
Hb (g/dL)	7.74	8.23	9.26	13.24	14.98
RBC (M/µL)	6.8	7.1	7.7	9.8	10.8
HCT (%)	33.8	33.8	38.7	42.2	45.5
MCV (fL)	49.6	48	51.0	43.0	42.4
Platelet (K/µL)	696	580	488	980	1182
Retics (%)	34.4	34.0	44.8	19.6	14.2
Abs Retics (K/µL)	2345	2381	3407	1911	1562
Spleen/Body Wt (%)	5.4	5.7	6.9	3.8	4.0

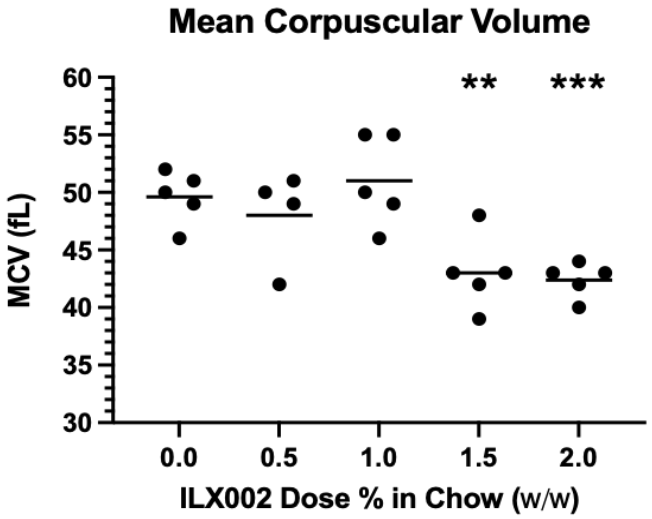
- ILX002 demonstrates dramatic dose-dependent improvements across all hematologic indices after 27 days
  - 100% of mice at 40% occupancy or greater achieved normal hemoglobin level ($\geq$13 g/dL)
  - Remarkable normalization of platelet count and reticulocytosis, approaching levels for healthy AA mice
  - Substantial reduction in relative spleen size without signs of extramedullary erythropoiesis
- Key findings in humanized SS mice strongly predictive of clinical responses in human SCD patients

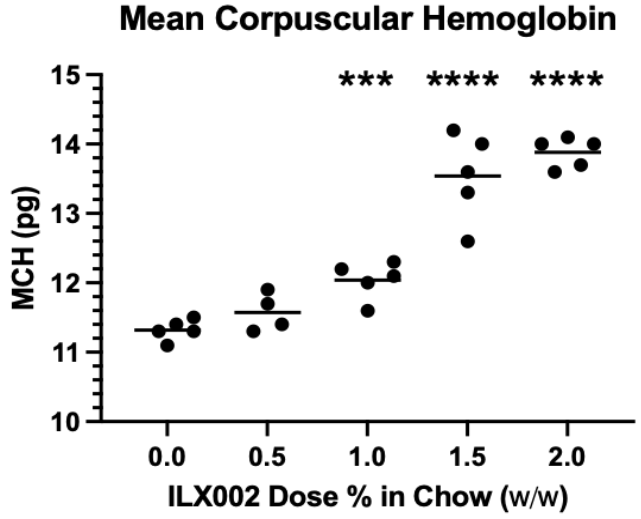
ILX002 Normalizes RBC Parameters (Day 27)

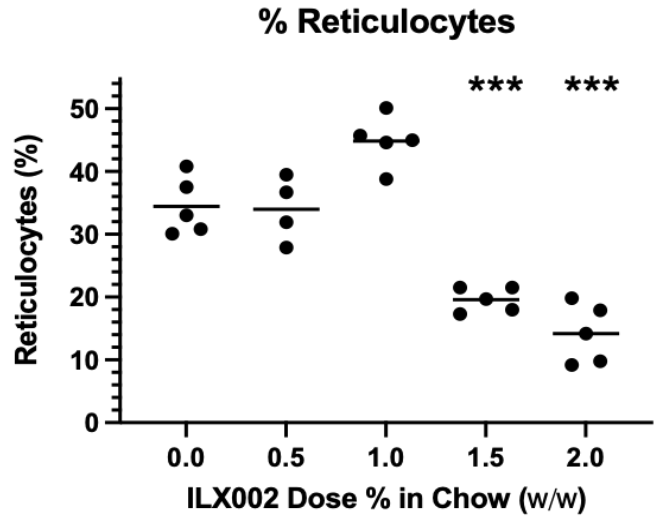








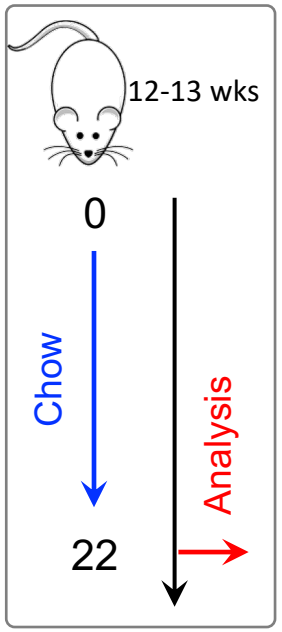




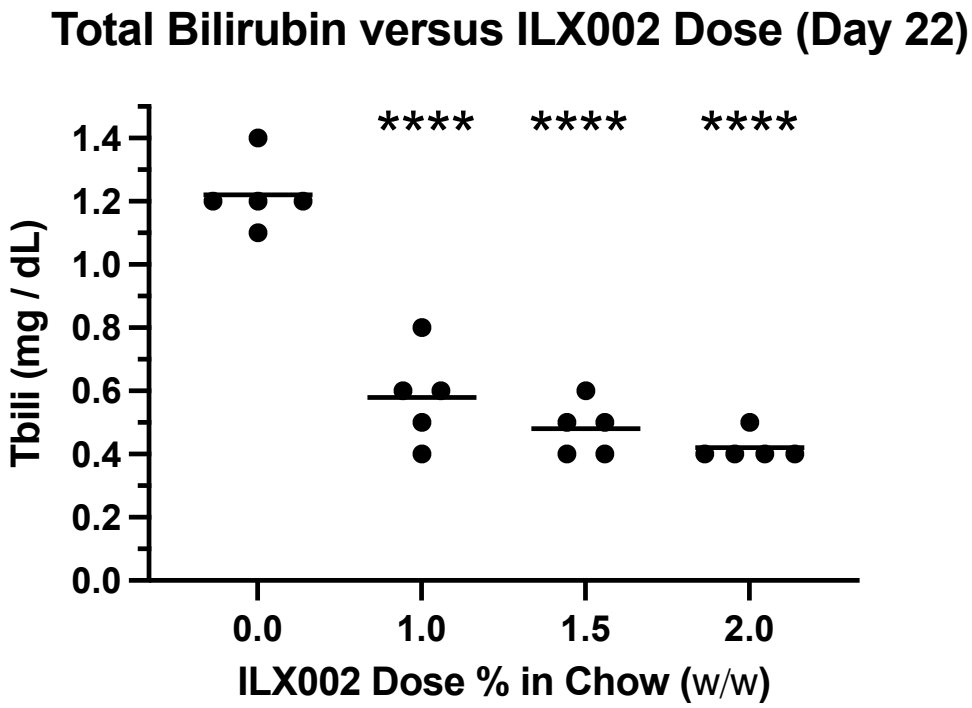
Dose-dependent improvement in RBC indices and reticulocyte count

mean, * p=0.03, ** p<0.006, *** p<0.0008, **** p<0.0001

ILX002 Decreases Hemolysis Markers



Humanized SS mice, n=5

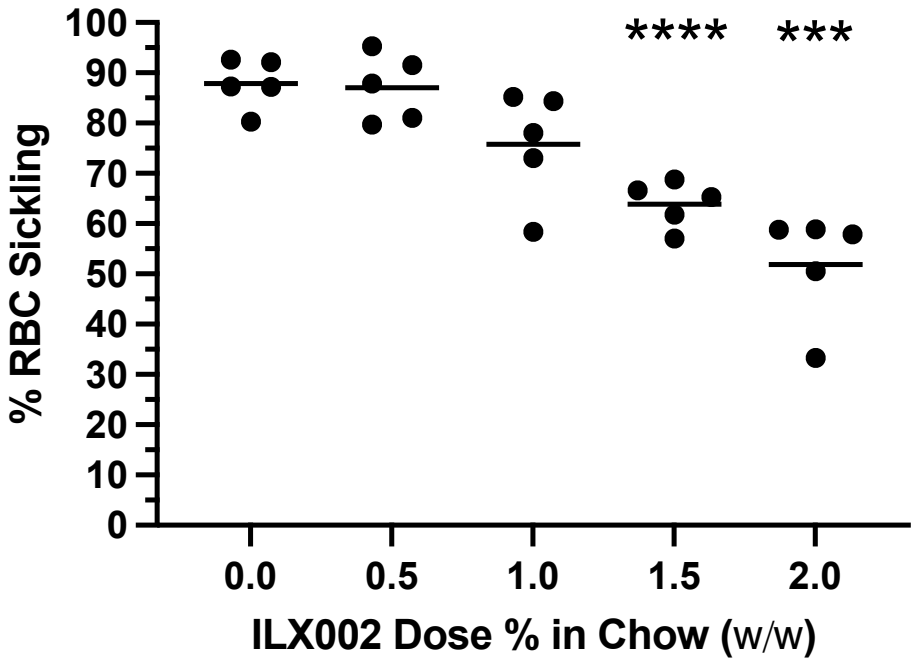


mean, ** p=0.0031, *** p=0.0005, **** p<0.0001

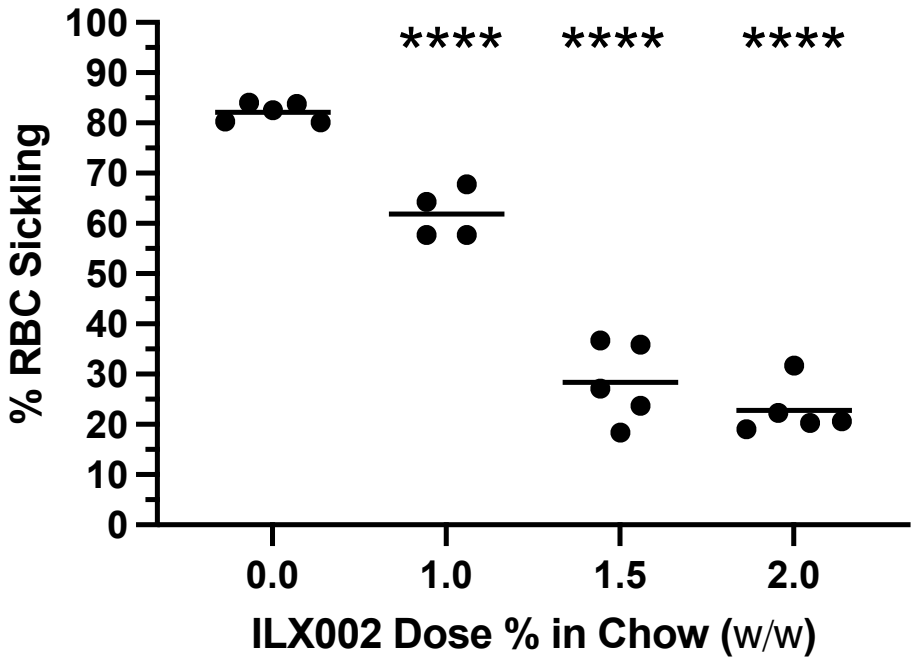
Decrease in hemolysis markers (60-70%) matches hemolysis reduction of *ex vivo* gene therapies

ILX002 Inhibits RBC Sickling Ex Vivo

Sickling in Anoxia (100% nitrogen gas, Day 27)



Sickling in Hypoxia (2.5% oxygen, Day 22)



Significant dose-dependent inhibition of RBC sickling *ex vivo*

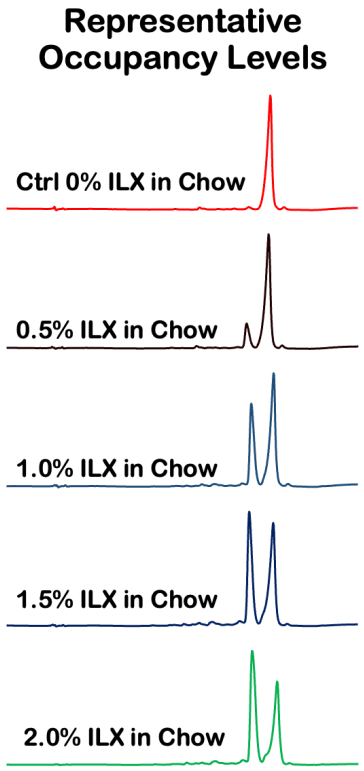
mean, *** p<0.0002, **** p<0.0001

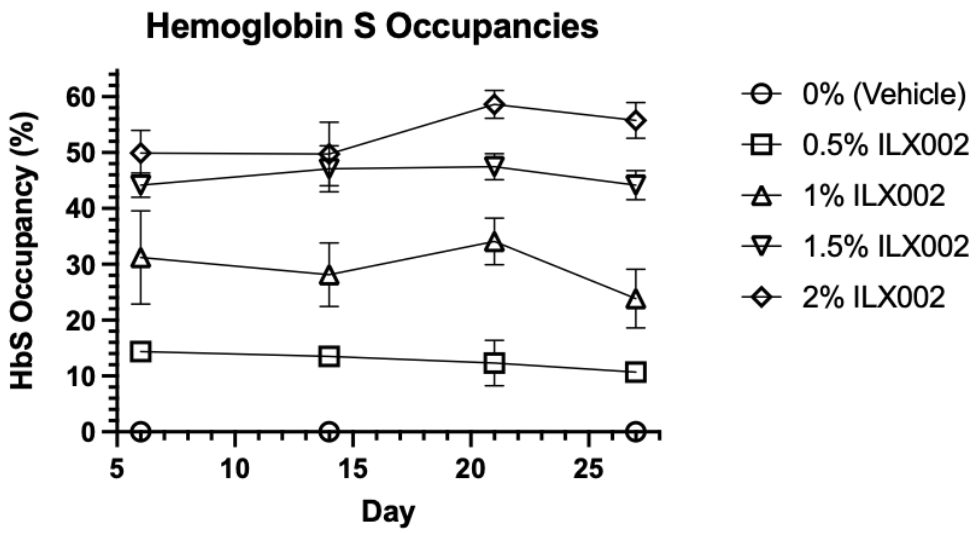
Abdulmalik O et al. *Sci Rep*. 2020; 10:20277.

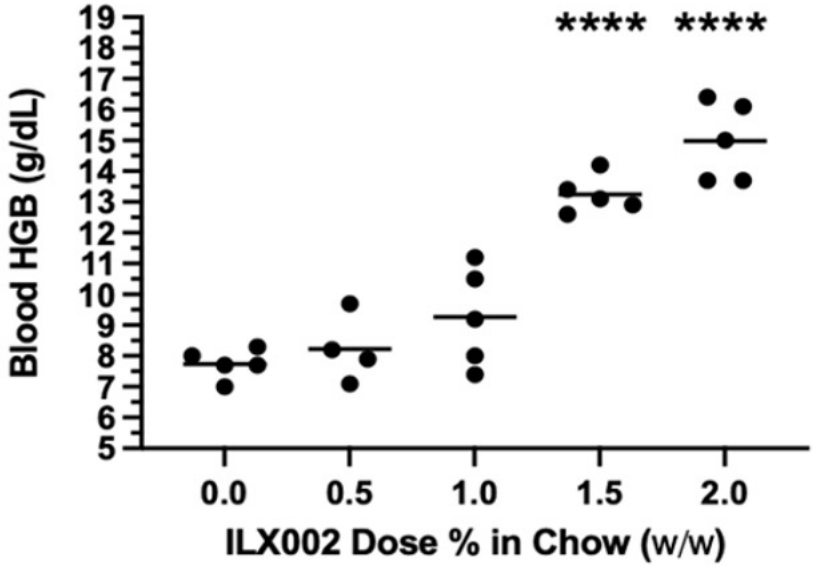
Small Molecules Targeting Hemoglobin

- How can we safely target such an abundant molecule like hemoglobin?
  - Healthy adults have a hemoglobin concentration of about 2 mM in the blood
- Naturally occurring aromatic aldehyde Vanillin (primary ingredient in extract from vanilla beans) forms reversible covalent Schiff base interaction with N-terminal valine at the α-cleft of hemoglobin
- ILX002 is a synthetic pyridinyl-based aromatic aldehyde designed from the vanillin scaffold
  - 70-fold greater Hb binding affinity due to extensive H-bonding and hydrophobic interactions at the alpha cleft
  - ILX002 is rapidly taken up by RBCs and is largely RBC restricted (up to 7,000-fold gradient from blood to free plasma)

Dynamic Equilibrium Maintains Stable HbS Occupancy

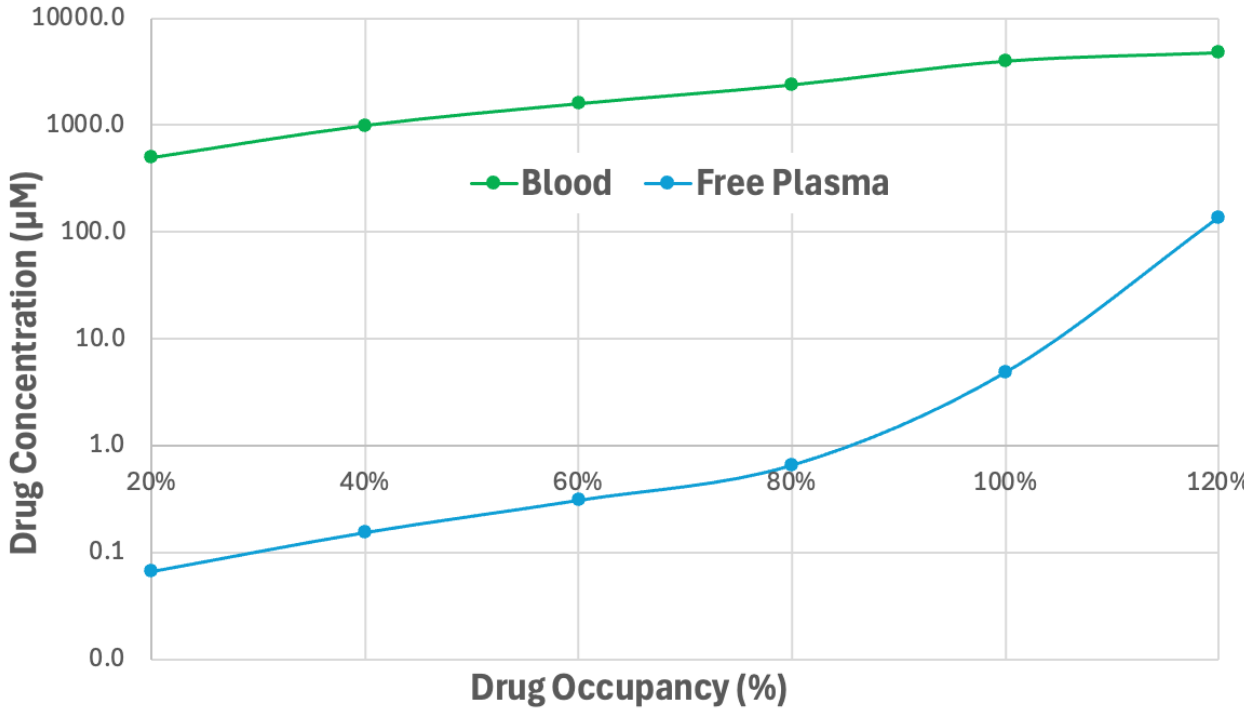


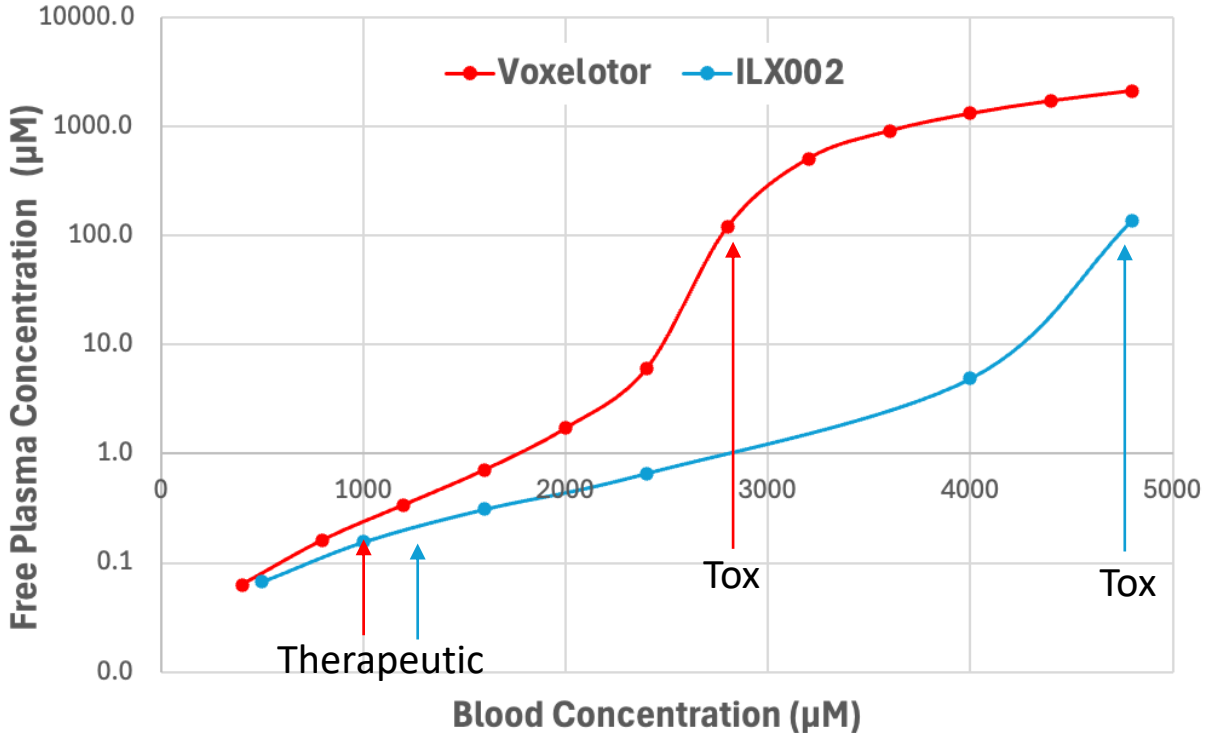




- Stable HbS occupancy despite increase in Hb levels during treatment in Townes mice
- Proportional shift of drug from plasma into RBCs results in compensatory decrease in drug elimination
  - Additional drug accumulation refills plasma compartment - no change in free or bound plasma drug levels

Hb Binding Capacity Increases Safety Margin

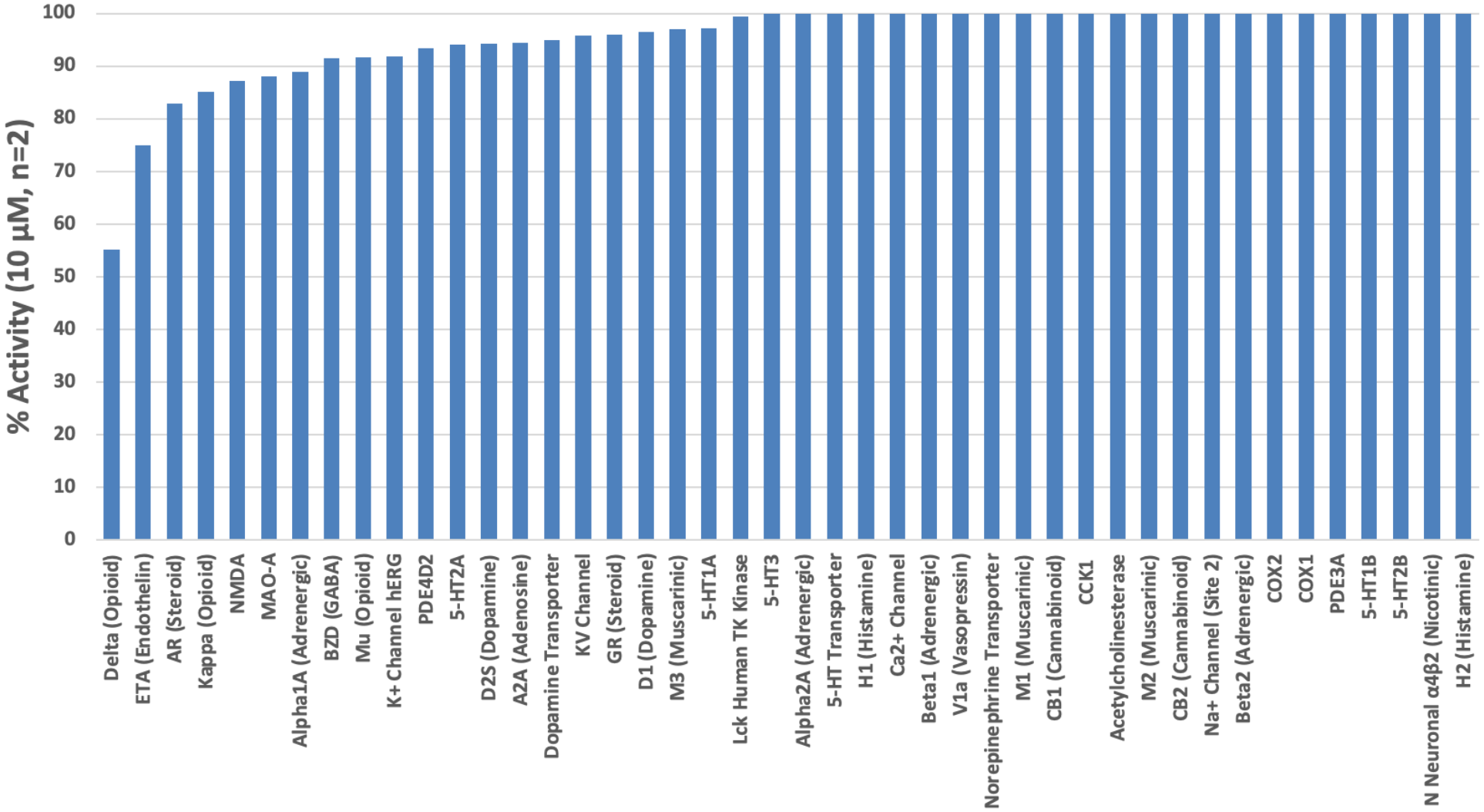




- Large safety margin for ILX002 due to significant excess of Hb binding capacity
  - 2-fold greater Hb binding capacity for ILX002 (4 mM) compared to Voxelotor (2 mM)
- Free plasma levels rise significantly once Hb is fully saturated
  - Generally safe in all species without overt toxicity until extreme blood levels exceed point of Hb saturation

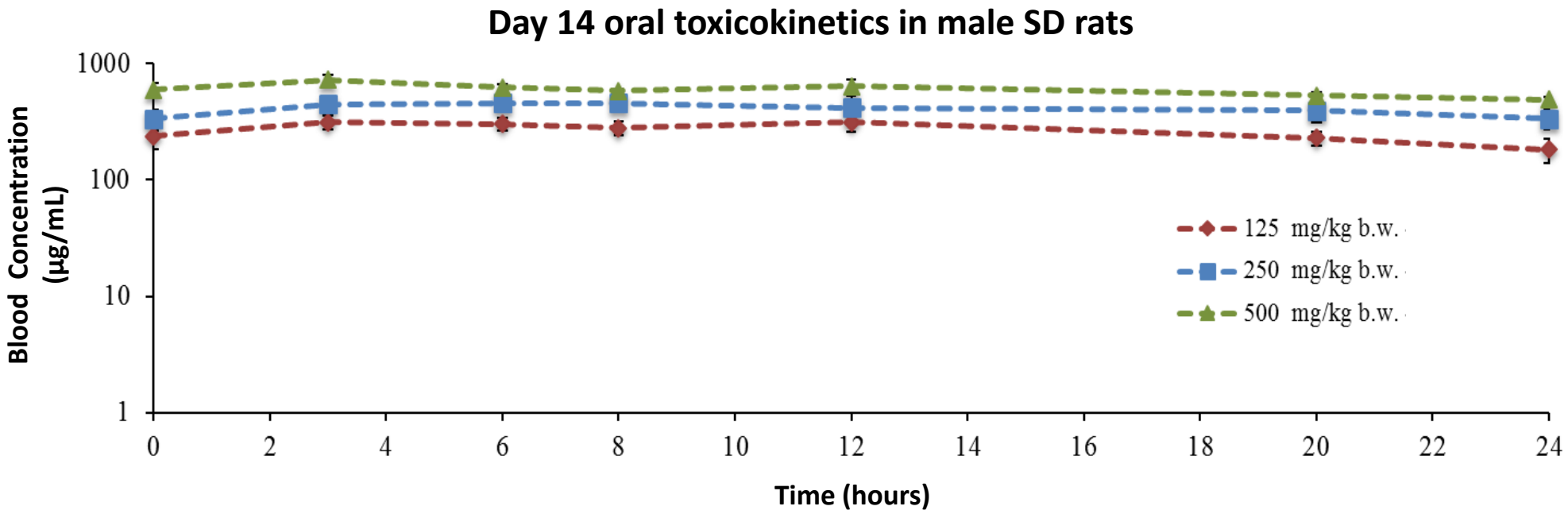
Data modeled based on relative K_D values

Safety Pharmacology Panel (10 µM)



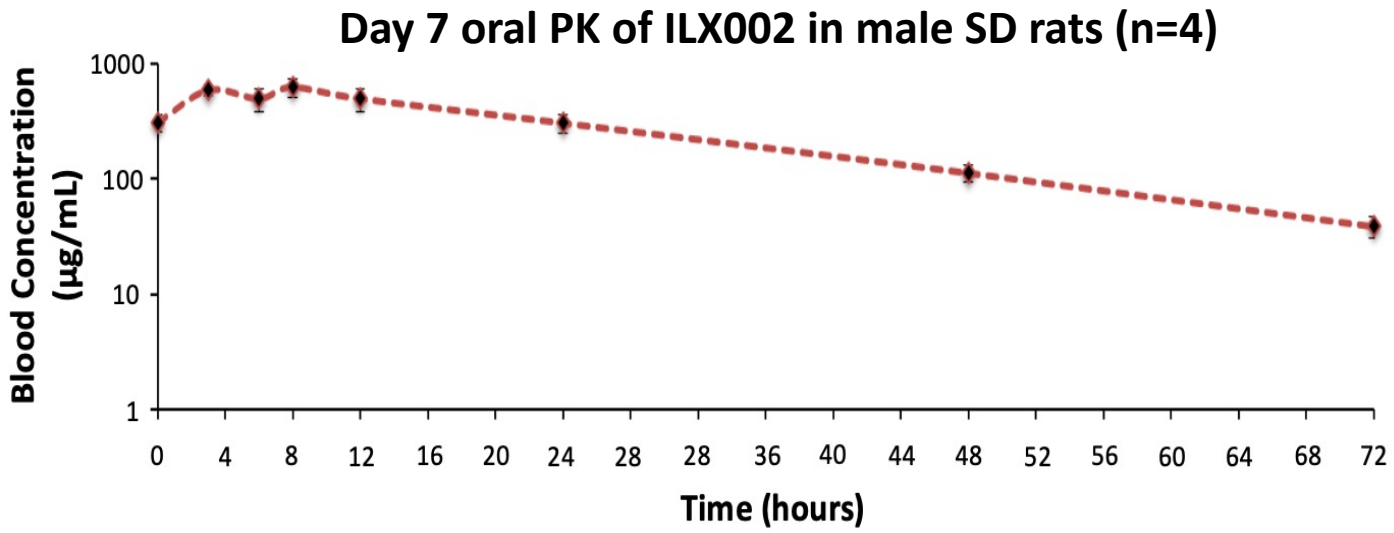
- No significant hits in safety pharma screen at > 30-fold above anticipated free plasma level

Non-Clinical Toxicology



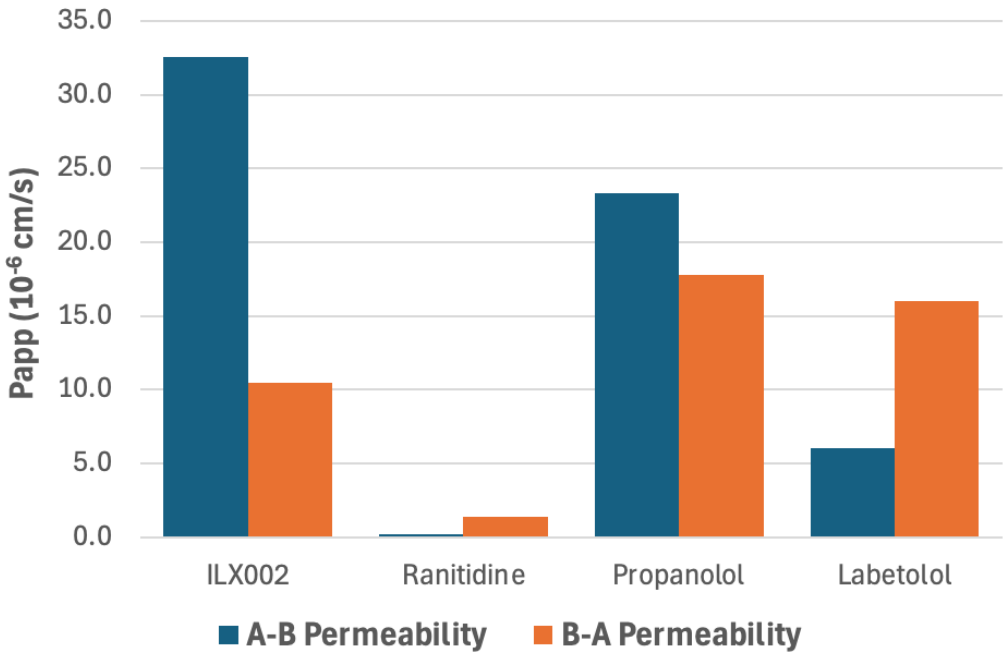
- Impressive toxicokinetic properties in escalating achieving blood concentrations up to 5 mM
- No significant adverse effects observed in rats below point of hemoglobin saturation (up to 4 mM)
  - Blood concentrations even in low dose cohort in SD rats exceeds anticipated therapeutic level
  - Free plasma levels at toxicologic threshold up to 1,000-fold above anticipated level in therapeutic range
- GLP toxicology (SD rat & beagle dog) and safety pharmacology studies in progress

ADME (Pharmacokinetics)



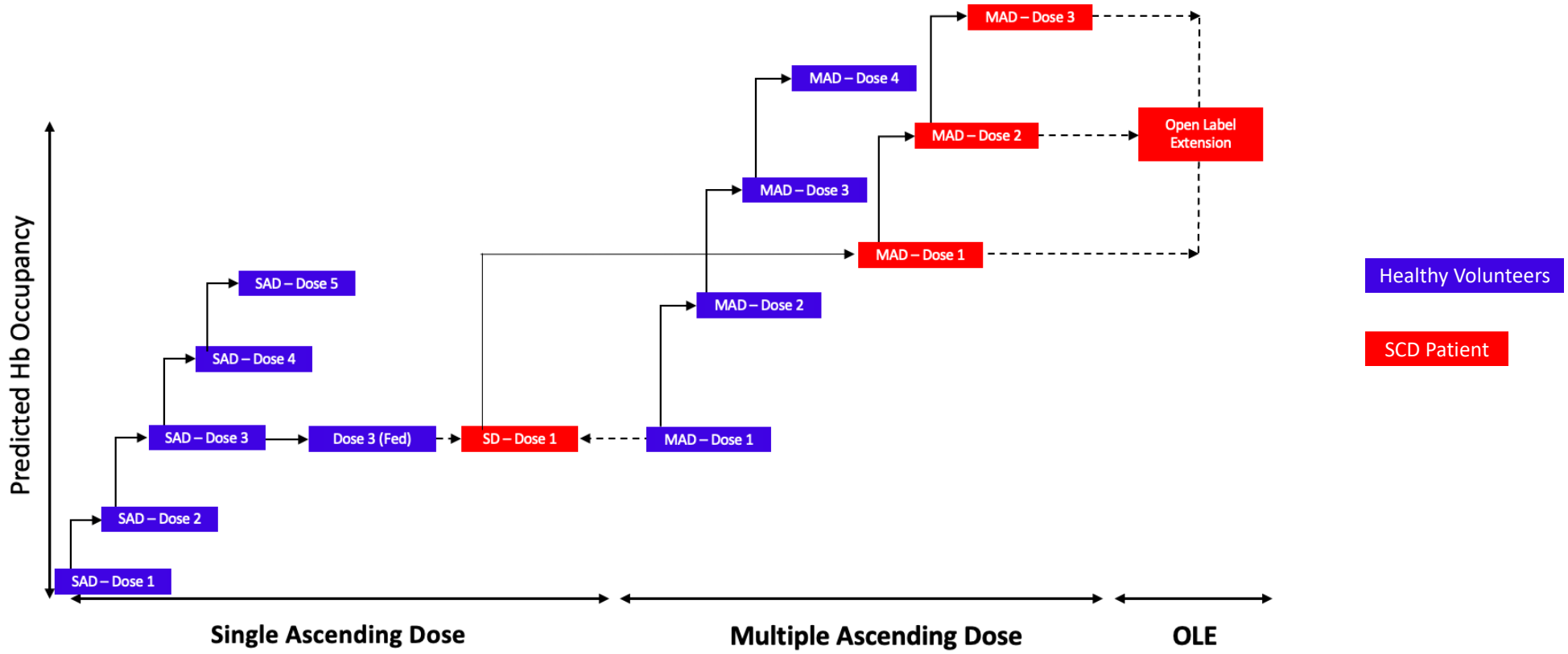
Dose (mg/kg)	C_{max} (µg/ml)	AUC_{0-24} (µg·h/mL)	$T_{1/2}$
125	656.8	11,183	16.3

MW - 229.2



- ILX002 has very high permeability and demonstrates robust exposure with extended $t_{1/2}$ in rodents
  - Allometric scaling projects to approximately 500 mg to 1 gram dose once daily in humans
  - Anticipated accumulation of 5-10-fold at steady state in human subjects

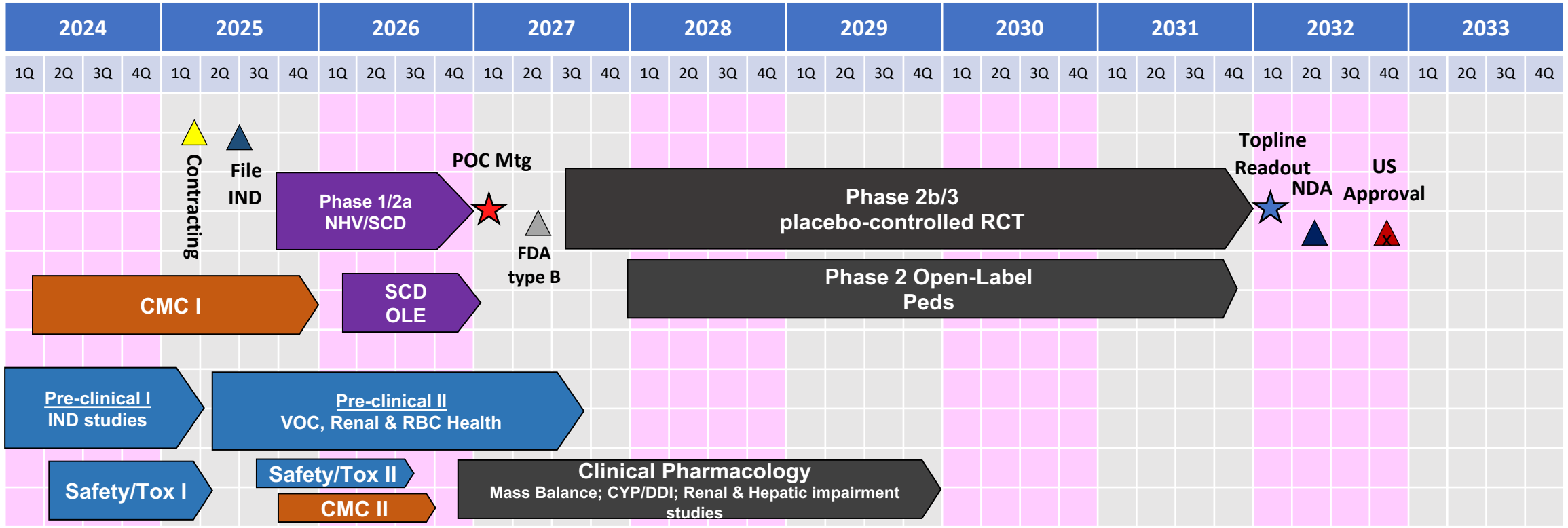
ILX002-001: First-in-Human Clinical Trial Plan



- Plan to begin enrollment of Phase I/IIa human clinical trial starting in 2025
  - Strategy to rapidly enroll 72 healthy volunteers in the US and 38 SCD patients in less than 12 months
  - Top line results, including 6-month extension, expected by early 2027
- End of Phase II meeting with US FDA in 2027 to align on pivotal Phase IIb/III registrational trial

ILX002: Proposed SCD Development Plan*

***timelines are for illustrative purpose only**



Pre-Clinical Studies:

- Safety/Toxicology I: (28-day Rat and Dog, Safety Pharma)
- Safety/Toxicology II: (13-week Rat and Dog)
- Pre-Clinical I (In vitro and in vivo pharmacology and efficacy)
- Pre-Clinical II (Additional SCD model studies – VOC, renal)

Phase 1/2a Study: (Target FPI July 2025)

- Safety; MOA POC; Dose for Ph2b
- Validation of exploratory biomarkers

OLE Study:

- 6-month safety / VOC pain events
- Validate personalized dose optimization

Proof of Concept Meeting: (Target prior to end of Q4 2026)

- Was target CFB Hb achieved? Was safety profile favorable?
- Candidate doses for Ph2b
- VOC trend from OLE

Proposed Milestones:

- Contract Final ($ through HV SAD1))
- HV SAD 2 ($ through FDA Type B)

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