



US STRATEGIC COUNCIL FOR DEMONSTRATING EFFECTIVENESS

October 20, 2023



WELCOME

2023 STRATEGIC COUNCIL



US STRATEGIC COUNCIL FOR DEMONSTRATING EFFECTIVENESS

GROUND RULES

As our advisor, please...

- Ensure confidentiality of this discussion
- Refrain from taking screenshots
- Provide open and candid feedback
- Engage in constructive discussion
 - Share your perspectives and build on those of your peers
 - Varied opinions are valued – consensus is not necessary

Housekeeping



Active attendees:

Please keep your video camera on while we are in session

Passive attendees:

Please keep your video camera off for the duration of the meeting



Active attendees:

Please keep your line muted when you are not speaking

Passive attendees:

Please keep your line muted for the duration of the meeting



Active attendees:

Feel free to use the *raise your hand* feature and the *chat* feature in Zoom

Passive attendees

can raise questions to active
may otherwise not talk



The meeting is being recorded to aid with a report for internal reference

Today's Objectives

- **Gene Therapies Landscape:**
 - Explore payers' points of view regarding the roles and coverage of currently-approved gene therapies
 - Identify key evidence requirements and likely coverage for gene therapies potentially to be approved in next five years.
- **Non-Alcoholic Fatty Liver Disease (NAFLD)-associated Hyperoxaluria:**
 - To understand payer perceptions of the residual unmet need for patients with NAFLD-associated Hyperoxaluria with Recurrent Kidney Stones and the implications for evidence requirements
 - To explore payer receptivity to an investigational therapy, **PRD 255**, and expected payer coverage across various potential development scenarios.

US Strategic Payer Council Advisors 2023

NAME	ORGANIZATION
Ed Pezalla, MD	Enlightenment BioConsult
Felicia Wade, MD	United Healthcare
James Bowerman, MD	Molina Healthcare
Joe Biskupiak, PhD	University of Utah School of Pharmacy
John Fox, MD	OneOncology
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Lon Castle, MD	Express Scripts EviCore
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Lynne Milgram, MD	Sharp Healthcare
Marc Dinnel, PharmD	Mercy Health Plan

Participants

Heather Ollison	Group Vice President, US Commercial
PJ Keith	Vice President, US Market Access
John Nelson	Director, US Pricing and Market Access Strategy
Joost Van Backle	Senior Director, Global Market Access, Pipeline/Gene Therapies
Johnny Chew	Associate Medical Director, Clinical Development
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Paul Okhuoya	Director, Global Market Access Lead, PRD 255
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Lee Blansett	HMP Market Access Insights (MODERATOR)
Cindy Chen	HMP Market Access Insights
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Samuel Amadi	HMP Market Access Insights
Corinne Cusumano	Mirada Life Sciences

Today's Agenda

FRIDAY, OCTOBER 20TH | 11:00AM—4:00PM PT

11:00-11:10	Lee Blansett	Organizational approach, ground rules, introductions
11:10-11:20	Heather Ollison	Overview of PRD Development/Pipeline
11:20-1:20	Johnny Chew/ Jolene Lau	Gene Therapy: Perception, Management and Planning for the future <ul style="list-style-type: none">• Current and pipeline landscape• Management of gene therapy• Value perception
1:20-1:40		Break
1:40-3:45	Thomas Morgan/ Carolina Amador	PRD 255: Non-Alcoholic Fatty Liver Disease (NAFLD)-associated Hyperoxaluria <ul style="list-style-type: none">• Disease background• Unmet need (therapeutic landscape)• Development plan: product profile, trial design and endpoints<ul style="list-style-type: none">• Large group discussion• Break out group discussion
3:45-4:00	Lee Blansett	Meeting recap, advisor feedback for 2023

PRD Development Pipeline

Research and Early Development	Product Candidate	Research	IND-Enabling	Phase 1	Phase 2
	BMN 255 Hyperoxaluria (Small Molecule)				
	BMN 351 DMD (Exon 51 Oligonucleotide)				
	BMN 349 A1ATD (Small Molecule)				
	BMN 333 Long Acting CNP (Peptide)				
	MSK (Oligonucleotide)	4 Candidates			
	MSK (Gene Therapy)				
	Metabolic (Biologic)	2 Candidates			
	HEM (Biologic)				
	HEM (Oligonucleotide)	2 Candidates			
	BMN 331 HAE (AAV Gene Therapy)				
	BMN 293 MYBPC3 HCM (AAV Gene Therapy)				
	BMN 365 PKP2 ACM (AAV Gene Therapy)				
	BMN 355 for LQT (Monoclonal Antibody)				
	CV (AAV Gene Therapy)	2 Candidates			
CV (Oligonucleotide)	2 Candidates				
CV (Monoclonal Antibody)					
CNS (AAV Gene Therapy)	4 Candidates				
CNS (Oligonucleotide)	3 Candidates				
CNS (Biologic)					

- Musculoskeletal (MSK)/Metabolic
- Non-Oncology Hematology
- Cardiovascular (CV)
- Central Nervous System (CNS)
- Other



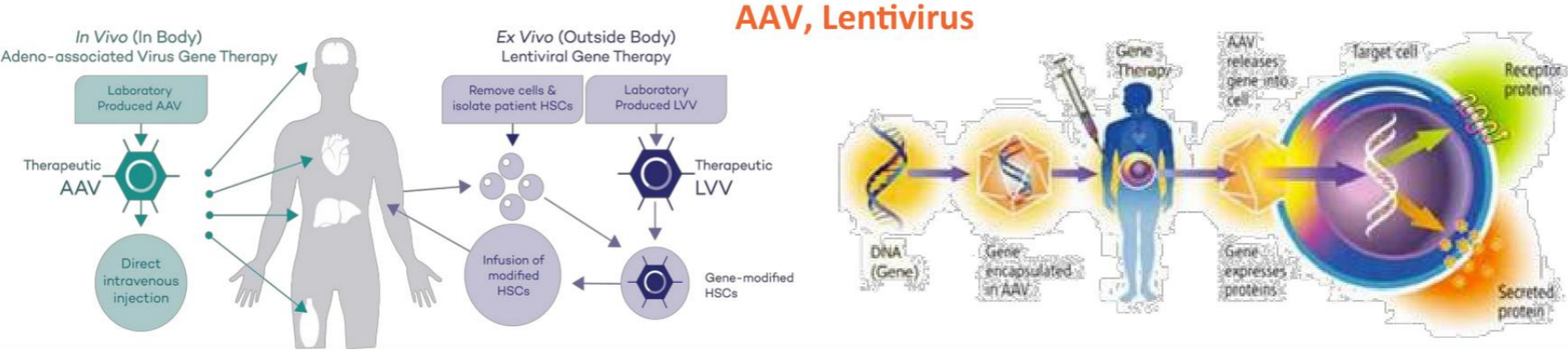
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GENE THERAPY

Gene Therapy Platforms

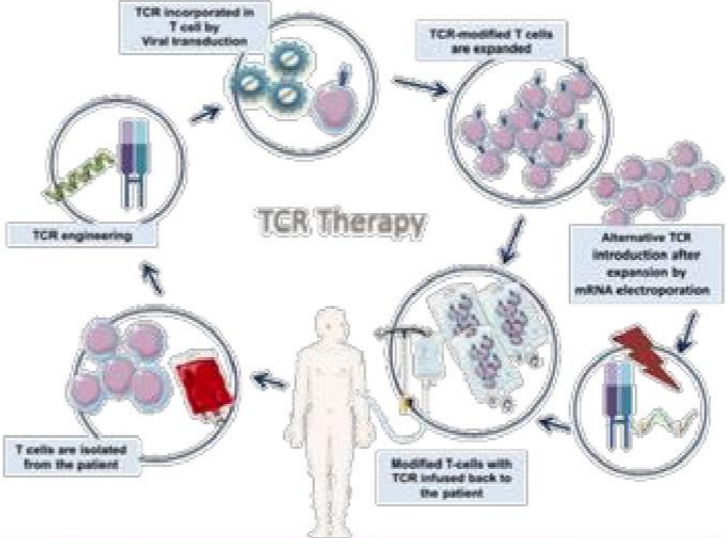
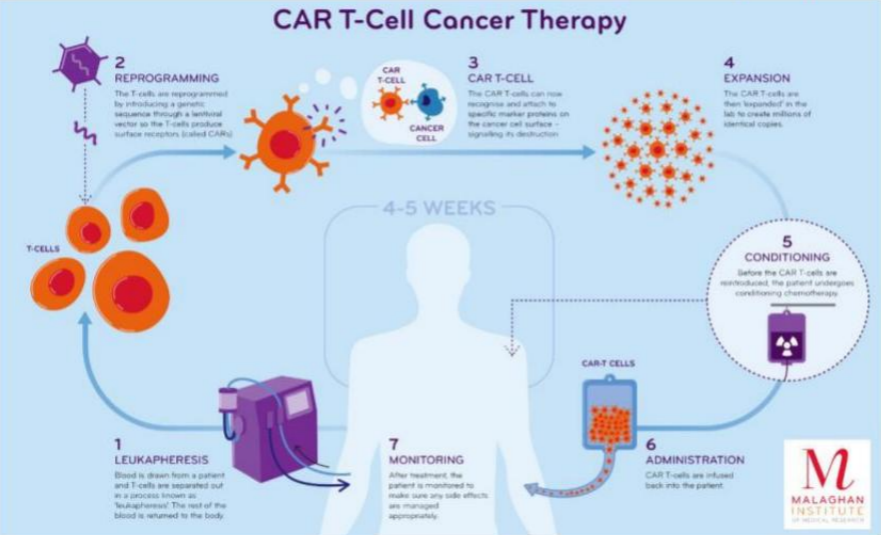
Gene Therapy Platforms

Gene replacement (viral vectors)



Genetically modified cell-based immunotherapies

CAR T cell therapies, TCR therapies, NK cell therapies

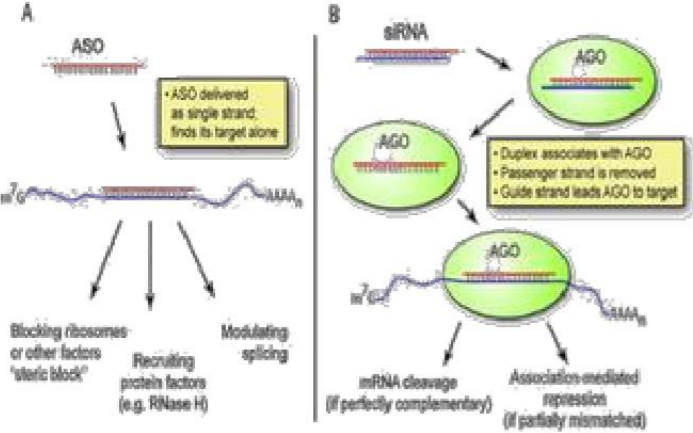


Gene Therapy Platforms

Gene Therapy Platforms

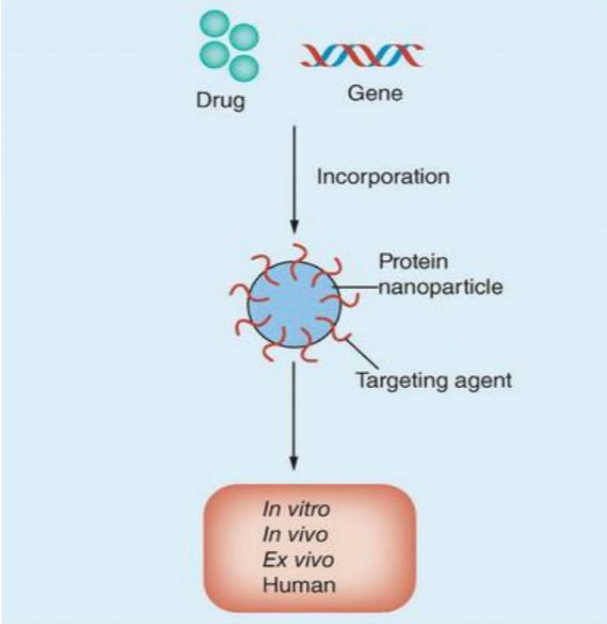
Gene Silencing

siRNAs, ASOs



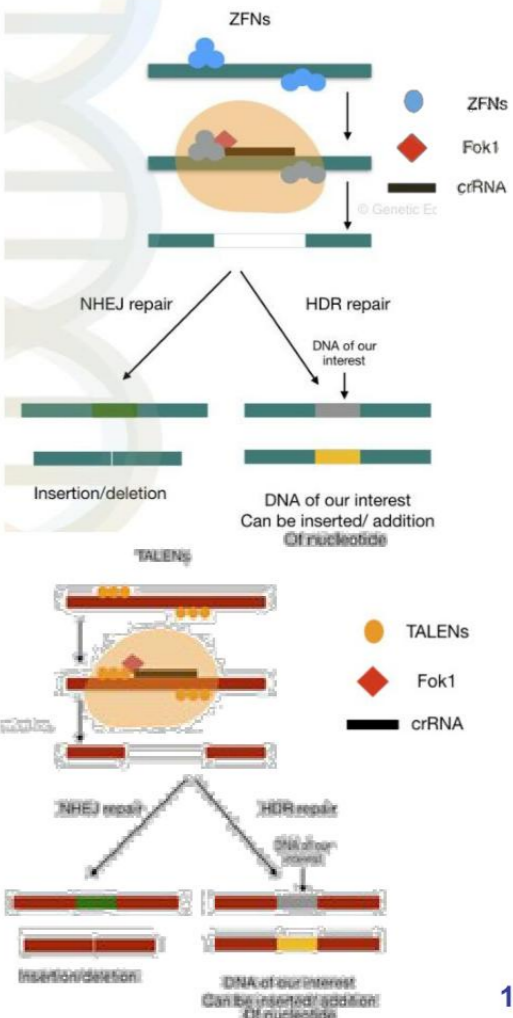
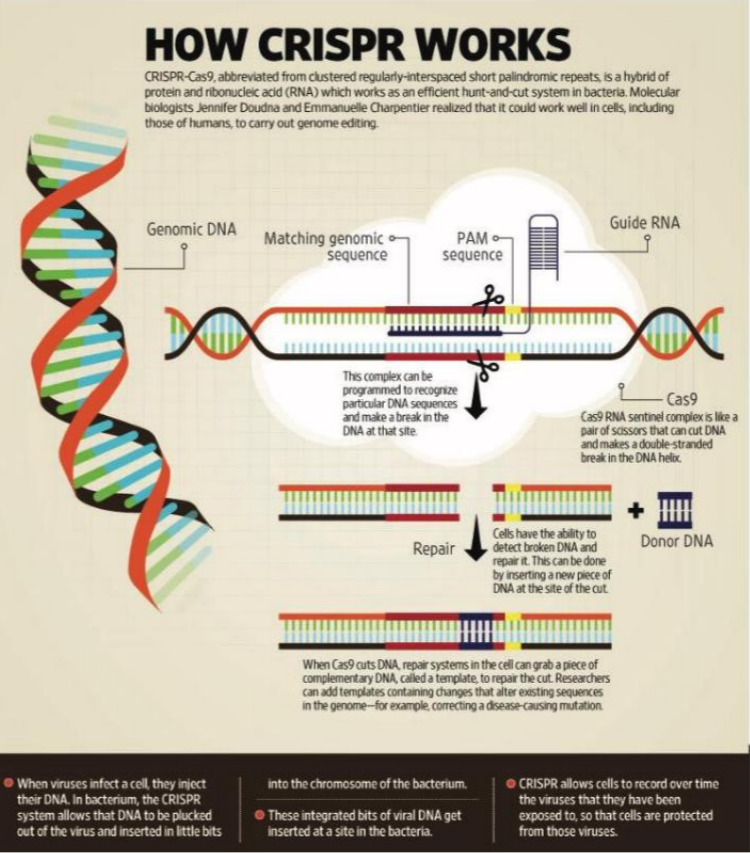
Non-viral vectors

Nanoparticles, Nanospheres

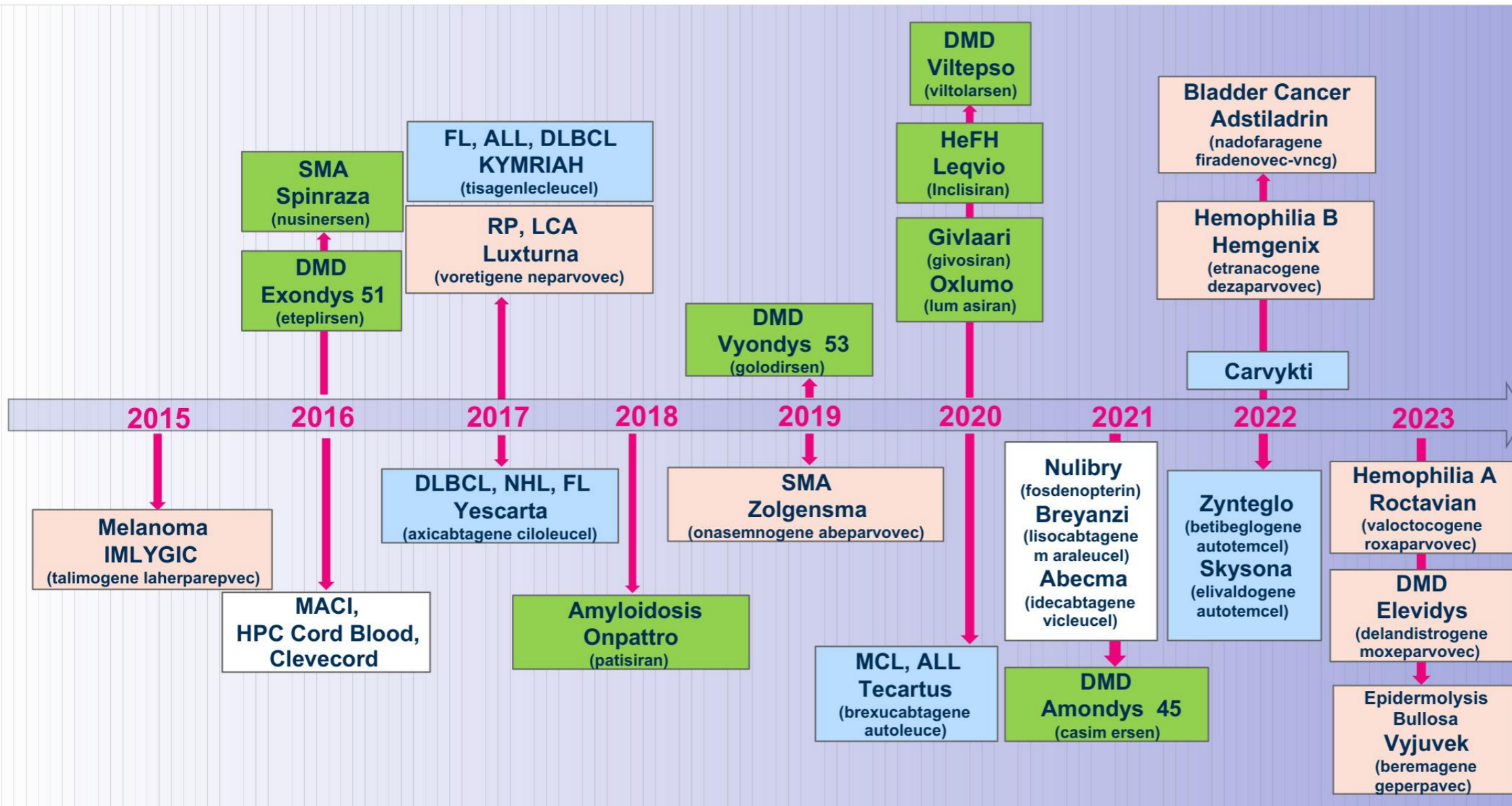


Gene Editing

CRISPR/Cas, Zinc finger nucleases, TALENs



Gene Therapy Development and First Approvals Dates



Type of Gene Therapy Platform

- Multiple products, more than one platform
- Cell Therapy Based
- Gene Silencing
- Gene Replacement

Abbreviations

- SMA (Spinal muscular atrophy)
- DMD (Duchenne muscular dystrophy)
- DLBCL (Diffuse large B cell lymphoma)
- NHL (Non-Hodgkin's Lymphoma)
- FL (Follicular lymphoma)
- HeFH (Heterozygous familial hypercholesterolemia)
- MCL (Mantle cell lymphoma)
- ALL (Acute lymphocytic leukemia)
- RP (Retinitis pigmentosa)
- LCA (Leber's congenital amaurosis)

Select FDA Approved Gene Therapies (1/2)

	LUXTURNA (voretigene neparvovec-rzyl)	ZOLGENSMA (onasemnogene abeparvovec-xioi)	ADSTILADRIN (nadofaragene firadenovec-vncg)
Manufacturer	Spark Therapeutics	Novartis	Ferring Pharmaceuticals
FDA Approval date	2017	2019	2022
Indication	Biallelic RPE65 mutation-associated Retinal Dystrophy ²	Spinal Muscular Atrophy (Type I) ¹	Bladder Cancer ⁴
Key clinical data	<p>Study Design NCT00999609</p> <ul style="list-style-type: none"> Phase III, open-label, RCT N=31 patients, aged 3 or older¹ <ul style="list-style-type: none"> Intervention Arm (n=21): subretinal administration of AAV2-hRPE65v2 (voretigene neparvovec-rzyl) Control Arm (n=10): No intervention, uninjected¹ <p>Primary Endpoint</p> <ul style="list-style-type: none"> Multi-luminance Mobility Testing (MLMT)*, Bilateral (1-year change from baseline) <p>Secondary Endpoint</p> <ul style="list-style-type: none"> Full-field Light Sensitivity Threshold (FST) Testing: White Light (1-year change from baseline)¹ <p>Results</p> <ul style="list-style-type: none"> MLMT score change for bilateral eyes, median(min,max) <ul style="list-style-type: none"> Luxturna: 2(0,4)²; Control: 0(-1,2)² Luxturna's demonstrated efficacy at 1-year <ul style="list-style-type: none"> 55% of all participants had an MLMT score change of 2 or greater³ <p><small>*MLMT is a standardized, lab-based test where participants were observed navigating an obstacle course of varying height under different levels of illumination²⁻⁴</small></p>	<p>Study Design NCT03381729</p> <ul style="list-style-type: none"> Phase III, open-label, single-arm, single-dose N=22 patients, aged 6 months or younger^{1,2} Intervention: AVXS-101 delivered intravenously <p>Primary Endpoints</p> <ul style="list-style-type: none"> Independent sitting for at least 30 seconds (up to 18 months)¹ Event-free survival (14 months) <p>Secondary Endpoint</p> <ul style="list-style-type: none"> Ability to thrive (18 months)¹ <p>Results</p> <ul style="list-style-type: none"> Motor milestone: 59% of patients could sit independently for at least 30 seconds² Event free survival: 91% of patients were alive and did not need permanent breathing support² 64% of patients could sit without support for at least 30 seconds at any point in the study^{2*} <p><small>*One patient sat independently for 30 seconds or more at 16 months of age, but this milestone was not reconfirmed at the 18 months of age study visit (end of study)²</small></p>	<p>Study Design (NCT02773849)</p> <ul style="list-style-type: none"> Phase III, open-label, multicenter, single-arm study N=157 patients, aged 18 or older Population: high-risk, Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS)¹ Intervention: Adstiladrin delivered intravesically <p>Primary Endpoint</p> <ul style="list-style-type: none"> Number of patients with CIS with a complete response (CR) (12 months)¹ <p>Secondary Endpoint</p> <ul style="list-style-type: none"> Durability of CR in patients with CIS (up to 60 months)⁴ <p>Results</p> <ul style="list-style-type: none"> 51% of the CIS cohort achieved CR, all by 3 months¹ Duration of response*: 9.7 months (median); % of patients with duration ≥12 months: 46%¹ During the 12-month study period²: <ul style="list-style-type: none"> 96% of patients did not progress to MIBC 74% of patients were cystectomy free 36% of patients remained free of high-grade recurrence up to 2 years. <p><small>*Based on patients (n=50) who achieved a CR; reflects period from the time CR was achieved.¹</small></p>
Price	\$425K (per eye) one-time treatment	\$2.1M WAC	\$60k per administration, every 3 months (quoted cash price)

Select FDA Approved Gene Therapies (2/2)

	HEMGENIX (etranacogene dezaparavovec-drib)	Vyjuvek (beremagene geperpavec)	ELEVIDYS (delandistrogene moxeparvovec)	ROCTAVIAN (valoctocogene roxaparvovec-rvox)
Manufacturer	CSL Behring	Krystal Biotech	Sarepta Therapeutics	BioMarin
FDA Approval date	2022	2023	2023	2023
Indication	Hemophilia B (congenital Factor IX deficiency)	Dystrophic Epidermolysis Bullosa (DEB)	Duchenne Muscular Dystrophy (DMD)	Hemophilia A (congenital factor VIII deficiency)
Key clinical data	<p>Study Design NCT03569891</p> <ul style="list-style-type: none"> Phase III, open-label, single-dose, RCT N=54 patients² Experimental arm: A single infusion of AAV5-hFIXco-Padua (AMT- 061)! Active comparator:FIX replacement ¹ <p>Primary Endpoint</p> <ul style="list-style-type: none"> Annualized bleeding rate (ABR)¹ <p>Secondary Endpoint</p> <ul style="list-style-type: none"> Factor IX Activity Levels after AMT-061 <p>Results</p> <ul style="list-style-type: none"> 54% reduction of all bleeds on Hemegenix (average of 4.1 ABR while on factor IX prophylaxis; 1.9 ABR on Hemegenix)² 37% average factor IX sustained increase in 2 years on Hemegenix 63% reported zero bleeds in the 7 to 18-month period following Hemegenix 94% of Hemegenix patients remained prophy-free.² 	<p>Study Design NCT04491604</p> <ul style="list-style-type: none"> Phase III, intra-subject parallel study N=31 patients Experimental arm: Primary wound receives B-VEC Placebo comparator arm: Primary wound receives placebo <p>Primary Endpoint</p> <ul style="list-style-type: none"> Primary wound with 100% wound closure on Weeks 22 and 24 or Weeks 24 and 26 ¹ <p>Secondary Endpoint</p> <ul style="list-style-type: none"> Primary wound with 100% wound closure on weeks 8 and 10 or weeks 10 and 12 ¹ <p>Results</p> <ul style="list-style-type: none"> Vyjuvek demonstrated a significantly higher percentage of complete wound healing compared with placebo² Of the wounds treated with Vyjuvek that were closed at 3 months, 67% were also closed at 6 months ³ 	<p>Study Design Phase 1&2 (SRP-9001) NCT03769116</p> <ul style="list-style-type: none"> Study 1: Multi-center study including: <ul style="list-style-type: none"> Part 1: 48-week, randomized, double-blind, placebo-controlled period ¹ Part 2: 48-week period that began following completion of Part 1.¹ Study 2: Open-label, multi-center study with a cohort of 20 ambulatory male DMD subjects aged 4 through 7 years. <p>Primary Endpoints for Study 1: Expression of Elevidys micro-dystrophin in skeletal muscle and effect of Elevidys on the North Star Ambulatory Assessment (NSAA) total score ¹</p> <p>Primary Endpoints for Study 2: Effect of Elevidys micro-dystrophin expression ¹</p> <p>Results¹</p> <p>Mean Elevidys micro-dystrophin expression levels (change from baseline) at Week 12 following infusion for patients 4 to 5 were:</p> <ul style="list-style-type: none"> 95.7% (N=3, SD: 17.9%) in Study 1 51.7% (N=11, SD: 41.0%) in Study 2 	<p>Study Desig(PRD 270-301) NCT03370913</p> <ul style="list-style-type: none"> Phase III, open-label, single-arm study N=112 patients Population: Hemophilia A patients With residual FVIII Levels ≤ 1 IU/dL receiving prophylactic FVIII infusions¹ <p>Primary Endpoint</p> <ul style="list-style-type: none"> Change in FVIII activity post-PRD 270 infusion³ <p>Secondary Endpoints</p> <ul style="list-style-type: none"> Change in the annualized utilization of exogenous FVIII replacement³ Change in the annualized number of bleeding episodes requiring FVIII replacement treatment³ <p>Results^{1,2}</p> <p>Annualized bleeding rate (ABR) and events:</p> <ul style="list-style-type: none"> 52% mean ABR reduction post Roctavian (2.6 bleeds/year vs 5.4 bleeds/year baseline)² Roctavian ABR: 0.5 bleeds/year for spontaneous bleeds and 0.6 bleeds/year for joint bleeds Baseline ABR on FVIII prophylaxis: 2.3 bleeds/year for spontaneous bleeds and 3.1 bleeds/year for joint bleeds²
Price	\$3.5 M (WAC) per one-time dose, flat pricing	\$631K per patient per year (\$24,250 per vial)	\$3.2 M (WAC), flat pricing	\$2.9 M (WAC) average per patient, weight-based

Group Discussion

PERCEPTION & MANAGEMENT (OF CURRENT GENE THERAPIES)

- Have you reviewed/authorized any of the currently available gene therapies?
- What kinds of advantages are current gene therapies providing for patients? For payers?
- Does your plan have an overall gene therapy management strategy or is it ad hoc, one product at a time?
- What is your current coverage policy and management strategy for gene therapies/gene therapy platforms?
 - How do you prioritize or manage coverage for gene therapies?
 - Who's involved in managing/overseeing coverage?

Please tell us what you think: Polling

- Poll #1
- Poll #2

Elevidys: Accelerated approval in pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD)

Accelerated approval was primarily based on data from Study 1* and Study 2* described below:

- A multicenter randomized, double-blind, placebo-controlled study of delandistrogene moxeparvec (SRP-9001) for Duchenne Muscular Dystrophy (DMD)
- **Outcome: Elevidys increased the expression of the Elevidys micro-dystrophin protein in individuals aged 4 to 5 years with DMD.**

Primary Endpoints:

- Change at week 12 in SRP-9001 dystrophin protein expression (Western Blot Assay) (Study 1 and Study 2)
- Change at week 48 in North Star Ambulatory Assessment (NSAA) Total Score (Study 1)

Study	Trial Design	% of ELEVIDYS Micro-Dystrophin Expression Compared to Control at Week 12 (Western Blot Assay) ^{abc}			
		Study 1 Part 1	Study 1 Part 2	Study 2 Cohort 1	
Study 1*	<ul style="list-style-type: none"> • Part 1: a 48-week, randomized, double-blind, placebo-controlled period • Part 2: a 48-week period that began following the completion of Part 1. Patients who received placebo during Part 1 were treated with ELEVIDYS, and patients treated with ELEVIDYS during Part 1 received placebo. <p>Patients were randomized to receive either ELEVIDYS (N=20) or placebo (N=21). In the ELEVIDYS group, 8 patients received 1.33×10^{14} vg/kg of ELEVIDYS, and 12 patients received lower doses.</p> <p>Primary objective: To evaluate expression of ELEVIDYS micro-dystrophin in skeletal muscle, and to evaluate the effect of ELEVIDYS on the North Star Ambulatory Assessment (NSAA) total score.</p>	Mean change from baseline (SD) Patients 4-7 yrs	43.4 (48.6) n=6	40.7 (32.3) n=21	54.2 (42.6) n=20
		Mean change from baseline (SD) Patients 4-5 yrs	95.7 (17.9) n=3		51.7 (41.0) n=11
		Change in NSAA Total Score at Week 48 (Study 1)^d			
Study 2*	<p>Cohort study of 20 ambulatory male DMD subjects aged 4 through 7 years. All 20 subjects have a confirmed frameshift mutation, canonical splice site mutation, or premature stop codon mutation in the DMD gene.</p> <p>Subjects received corticosteroids for DMD before infusion. All subjects had baseline anti-AAVrh74 antibodies titers <1:400 and received a single intravenous infusion of 1.33×10^{14} vg/kg ELEVIDYS.</p> <p>Primary objective: Evaluate the effect of ELEVIDYS micro-dystrophin expression.</p>	Least squares mean change from baseline (SE) Patients 4-5 yrs	ELEVIDYS^e		Placebo
			4.3 (0.7) n=8	1.9 (0.7) n=8	
		<p>^a Change from baseline was statistically significant</p> <p>^b All patients received 1.33×10^{14} vg/kg, as measured by ddPCR</p> <p>^c Adjusted for muscle content. Control was level of wild-type (normal) dystrophin in normal muscle</p> <p>^d Data are from exploratory subgroup analyses</p> <p>^e Demonstrates a numerical advantage for ELEVIDYS compared to placebo</p>			

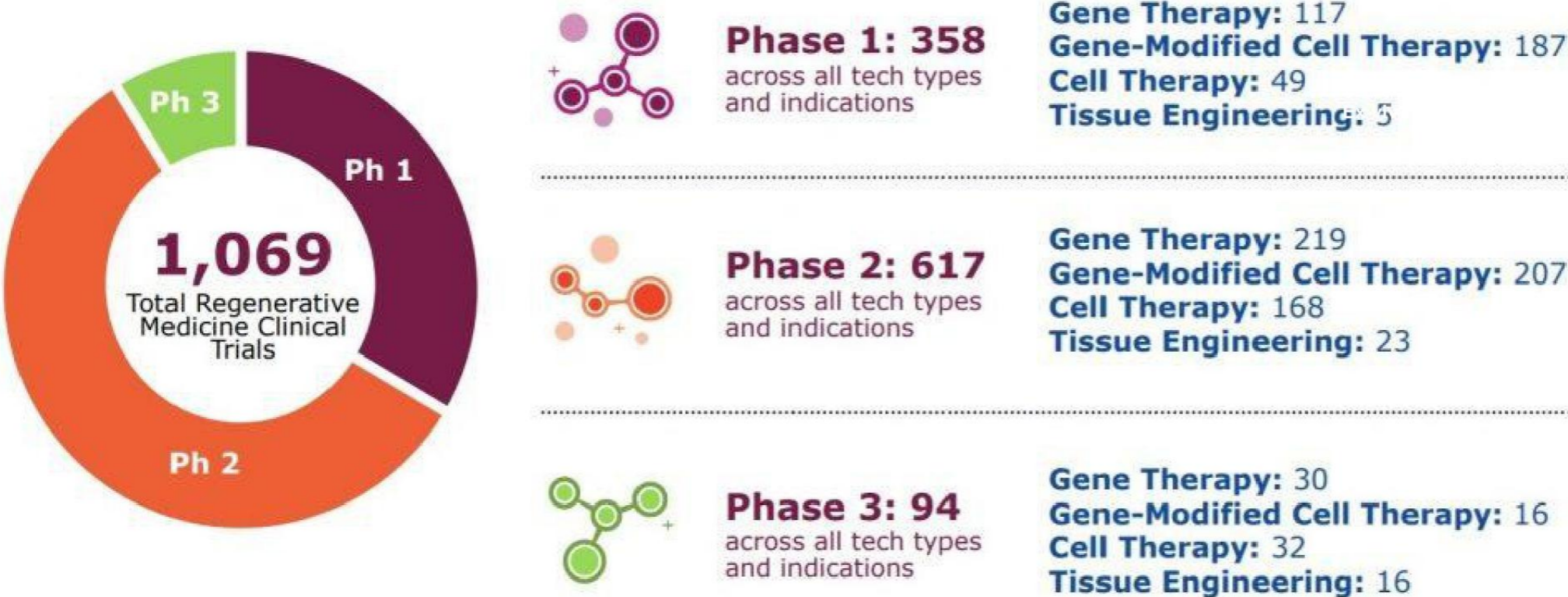
Group Discussion

PERCEPTION OF ELEVIDYS

- What is your perception in terms of clinical value based on Elevidys' clinical package?
 - What is your reaction to the change in micro-dystrophin levels? Is there value in the biomarker change?
 - Were the changes in NSAA scores in the approved population compelling in your decision to cover?
- Does your plan cover the recently approved Elevidys for DMD?
 - What were the most important factors that led to your coverage (or no coverage) decision? Are there any circumstances which may cause you to change your coverage decision?
 - How does the age limitation on label impact your management? Are you covering beyond 4th to 6th birthdays?
 - Does its accelerated approval impact your perception or management?

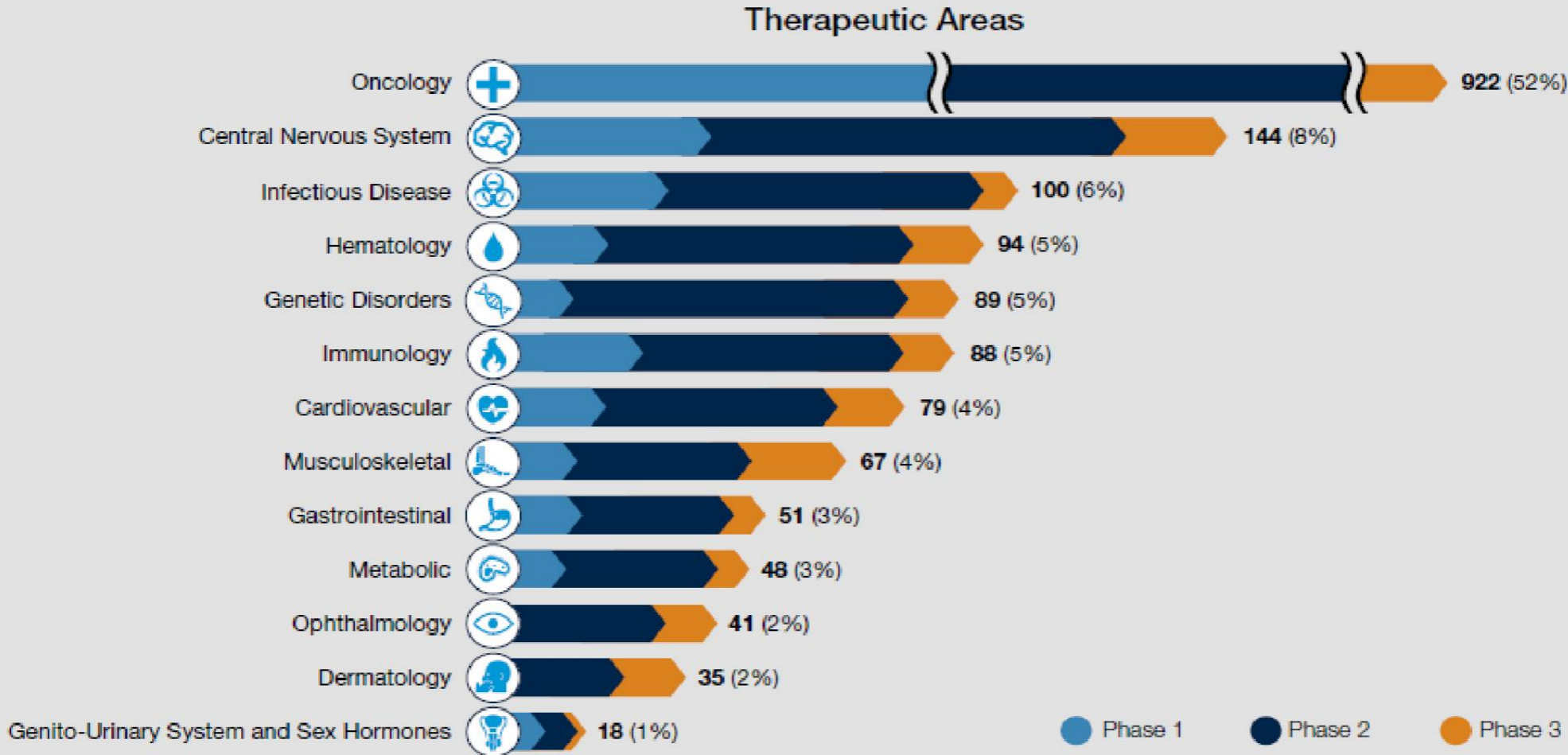
Potential Gene Therapy Pipeline by Platform (as of 2020)

Regenerative Medicine Clinical Trials by Phase and Technology Type



Source: Dan S. In the pipeline: Surge of cell and gene therapies likely in 2020. Alliance For Regenerative Medicine. Available at: <https://bioprocessintl.com/bioprocess-insider/therapeutic-class/in-the-pipeline-surge-of-cell-and-gene-therapies-likely-in-2020/>

Percentage of Cell and Gene Therapy by Therapeutic Areas



1. Percentages (%) based on trials with known therapeutic areas; 317 trials with area unknown or unclassified
 2. Unlisted areas include known areas with small numbers (<10) of CGT trials including mouth/dental, ear-nose-throat, and unspecified male/female disorders

Source: Alliance for Regenerative Medicine, "Regenerative Medicine: The Pipeline Momentum Builds", September 2022

CGT (Cell and Gene Therapy)

Cell and Gene Therapy Pipeline Outlook

Therapy Name and Manufacturer	Type	Indication	Projected Approval Timing	Phase of Development
Lovo-cel (bluebird bio)	Gene Therapy	Sickle cell disease	December 2023	Pending Approval
Lifileucel (lovance)	Cell Therapy	Metastatic melanoma	November 2023	Pending Approval
NurOwn (BrainStorm Therapeutics Inc.)	Cell Therapy	Amyotrophic lateral sclerosis	December 2023	Pending Approval
CTX001 (Vertex Pharmaceuticals & CRISPR Therapeutics)	Gene Editing Therapy	Sickle cell disease, β -thalassemia	SCD: December 2023 β -thalassemia March 2024	Pending Approval
Fidanacogene elaparvovec (Pfizer/Spark Therapeutics)	Gene Therapy	The treatment of hemophilia B in adults	2024	Pending Approval
UX111 (fka ABO-102) Abeona Therapeutics/Ultragenyx Pharmaceutical)	Gene Therapy	The treatment of mucopolysaccharidosis type 3A (also known as Sanfilippo syndrome type A)	2024	Phase III
Fordadistrogene movaparvovec (Pfizer)	Gene Therapy	The treatment of ambulatory patients with Duchenne muscular dystrophy (DMD)	2025	Phase III
Giroctocogene fitelparvovec (Pfizer/Sangamo BioSciences)	Gene Therapy	The treatment of hemophilia A in adults	2025	Phase III
Resamirigene bilparvovec (Astellas Pharma/Audentes Therapeutics)	Gene Therapy	The treatment of X-linked myotubular myopathy in males aged younger than 5 years	2025	Phase I/II
Laruparetigene zosaparvovec (Applied Genetic Technologies Corp.)	Gene Therapy	The treatment of X-linked retinitis pigmentosa in males aged 8–50 years with a mutation in the RPGR gene	2025	Phase II/III

Group Discussion

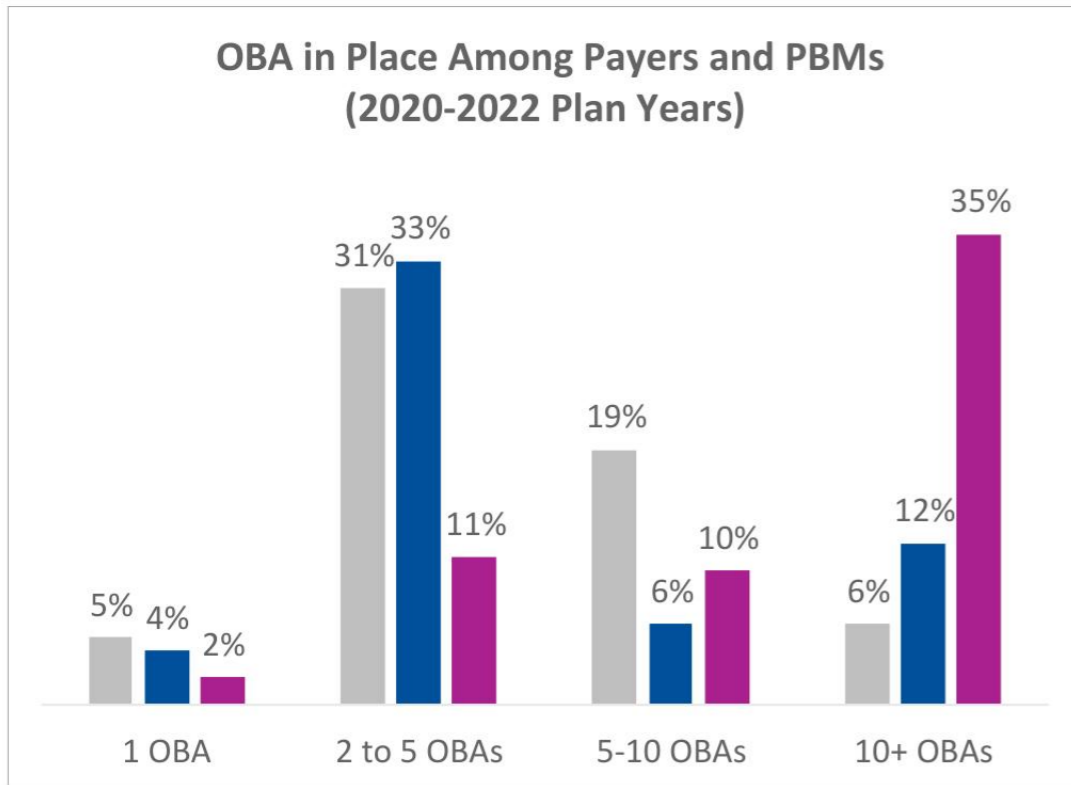
PLANNING FOR PIPELINE GENE THERAPIES

- What do you perceive as the key payer challenges as more gene therapy options become available in the next 2-5 years? What lessons (from current therapies) will be leveraged with new therapies?
- What has been your experience with the potential economic advantages of gene therapy? Have the potential cost offsets been realized with gene therapy?
- Will each new therapy be assessed on a “one-off” basis?
- What will happen if direct competition between two or more gene therapies emerges?
- What evidence constitutes the most compelling value arguments for gene therapies?
 - Does the type of gene therapy technology (e.g., AAV, lentivirus, CRISPR) change your perception of a potential treatment?
 - What would be considered compelling evidence if the primary endpoint is a biomarker?
 - Does the administration/treatment burden (e.g., in-patient, single infusion) impact your value perception?
- Do you anticipate a “holistic” review of manufacturers whose gene therapy might replace their existing products in the same therapeutic area (e.g., gene therapy and Factor XIII)?
- What do you believe are the major opportunities to improve the clinical value of future gene therapies?

Please tell us what you think: Polling

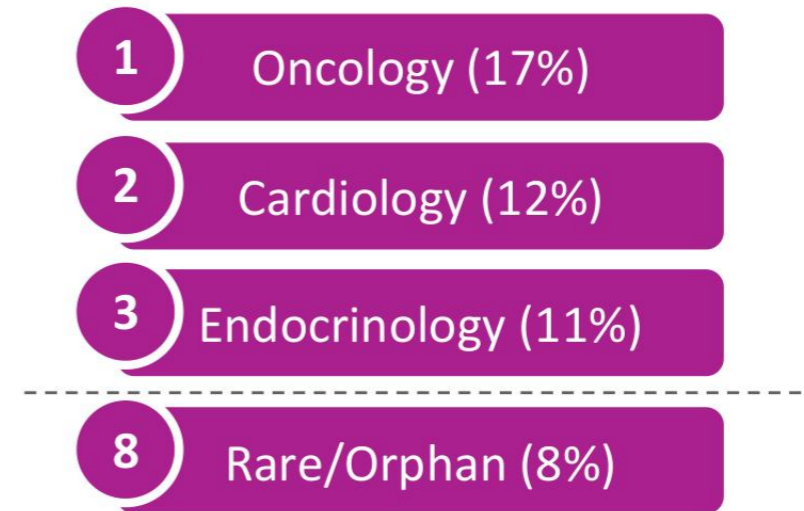
- Poll #4
- Poll #5

Percentage of payers using Outcomes-based Agreements (OBA) remain steady but volume of OBAs is increasing



	2020	2021	2022
% of payers/PBMs with at least 1 OBA	61%	55%	58%

Top Therapeutic Areas in Which OBAs Were Used (2022 Plan Year)



74% preferred agreements with both claims-based and clinical outcomes

Challenges with structuring OBAs

Frequently Cited OBA Challenges from Payers

- Assessing upfront risk due to limited/immature clinical data and uncertainty of real-world performance
- Determining appropriate time zone given fragmented, multi-payer system
- Agreement on appropriate endpoints and outcomes in contract negotiations
- Leveraging data infrastructure to measure relevant endpoints and outcomes
- Administrative burden to set up and implement vs. traditional rebates and discounts
- Missing infrastructure to store, measure and share patient data (often in niche or orphan disease areas)
- Increasing physician burden and reliance on physician reporting to determine outcomes

Select OBAs Currently in Place

LUXTURNA

Manufacturer: Sparks Therapeutics

Indication: biallelic RPE mutation-associated retinal dystrophy

Timeframe: 30-90 days and 30 months

Details: rebates tied to short-term efficacy and long-term durability based on light-sensitivity testing scores

ZOLGENSMA

Manufacturer: Novartis

Indication: spinal muscular dystrophy for pediatric patients less than 2 years of age

Timeframe: up to 5 years

Details: installment option over 5 years, dependent upon demonstrating continued performance over the period.

ZYNTEGLO

Manufacturer: bluebird bio

Indication: pediatric and adult β -thalassemia patients requiring regular red blood cell transfusions

Timeframe: up to 2 years

Details: single upfront payment with OBA in which payers will be reimbursed up to 80% if patient fail to achieve or maintain transfusion independence up to 2 years following infusion

Group Discussion

OUTCOMES BASED AGREEMENTS

- Has your plan entered (or plan to enter) into an outcomes-based agreement (OBA)? What are some key learnings or challenges you have experienced?
- What characteristics make OBAs worthwhile or feasible (e.g., price level, potential patients in plan, easy to monitor endpoints, etc.)?
- What do you perceive as an optimal construct for an OBA? Options may be rebates tied to efficacy, time-based patient response, pay-over-time with defined period? Individual patient vs. population/cohort-based agreements? Others?

Please tell us what you think: Polling

- Poll #6
- Poll #7

Today's Agenda

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11:20-1:20	Johnny Chew/ Jolene Lau	Gene Therapy: Perception, Management and Planning for the future <ul style="list-style-type: none">• Current and pipeline landscape• Management of gene therapy• Value perception
1:20-1:40		Break
1:40-3:45	Thomas Morgan/ Carolina Amador	PRD 255: Non-Alcoholic Fatty Liver Disease (NAFLD)-associated Hyperoxaluria <ul style="list-style-type: none">• Disease background• Unmet need (therapeutic landscape)• Development plan: product profile, trial design and endpoints<ul style="list-style-type: none">• Large group discussion• Break out group discussion
3:45-4:00	Lee Blansett	Meeting recap, advisor feedback for 2023

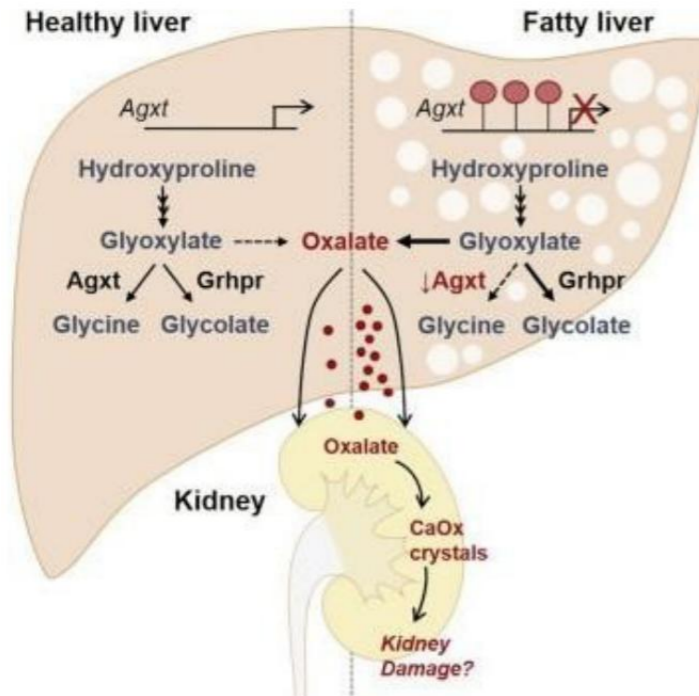


US STRATEGIC COUNCIL FOR DEMONSTRATING EFFECTIVENESS

**PRD 255 IN HYPEROXALURIA WITH
RECURRENT KIDNEY STONE FORMATION**

NAFLD-associated hyperoxaluria is a disorder characterized by elevated urinary oxalate levels due to AGXT downregulation and recurrent kidney stones

NAFLD-associated Hyperoxaluria Disease Overview and Pathophysiology



NAFLD causes downregulation of Agxt, a key enzyme used to detoxify glyoxylate. Such a downregulation causes oxalate accumulation, leading to elevated urinary oxalate levels²

Disease Description

- Disruption of normal metabolic function in the liver caused by NAFLD leads to excess oxalate accumulation in the urine
- Elevated urinary oxalate levels commonly lead to recurring kidney stones

Symptoms

- **Presentation with symptoms of kidney stones**, such as acute pain related to the groin or scrotum, as well as nausea and problems related to urination¹

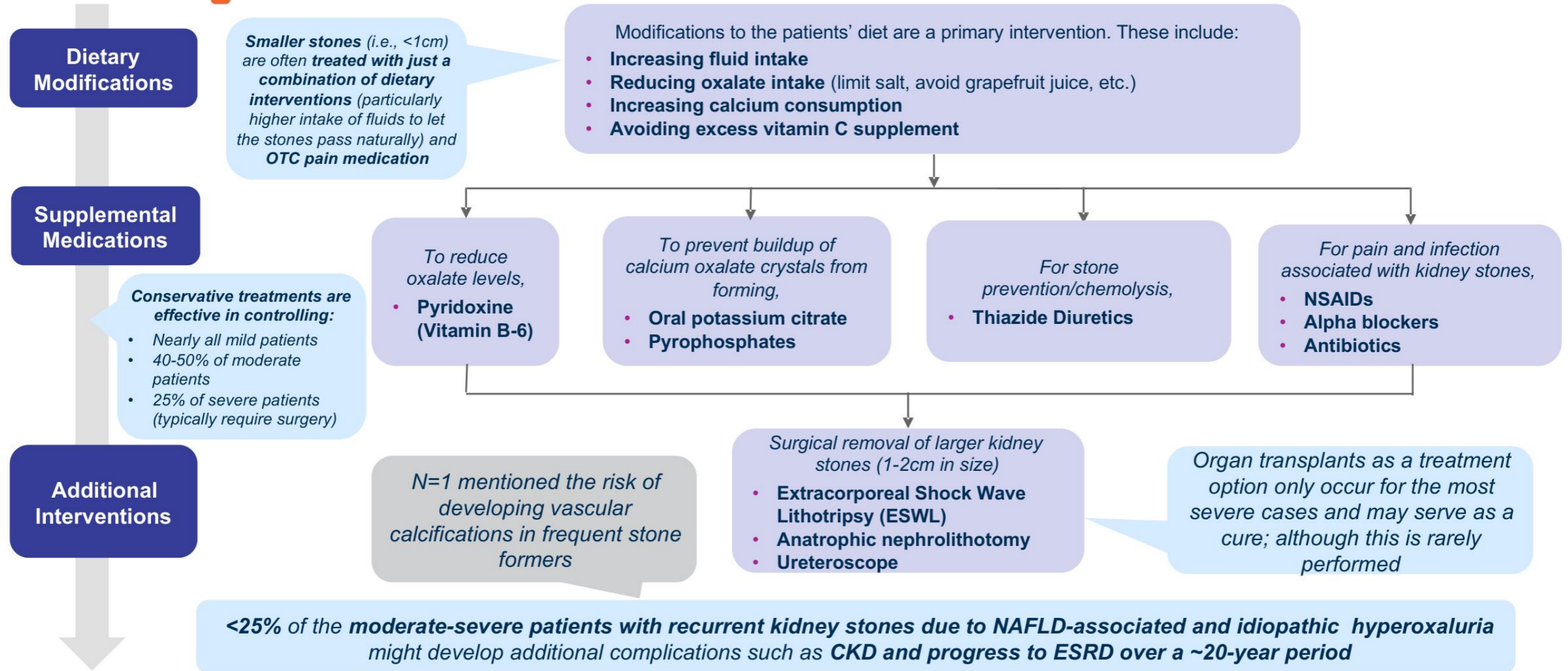
Etiology

- NAFLD-associated hyperoxaluria is caused by excess fat accumulation in the liver
 - Excess fat accumulation may cause downregulation of Agxt
- Downregulation of AGXT diminishes the capacity of the liver to detoxify and remove glyoxylate, causing oxalate accumulation, leading to elevated urinary oxalate levels²

Current treatment paradigm predominantly consists of dietary interventions layered with drug therapy to mitigate oxalate buildup



Treatment approach is consistent regardless if the hyperoxaluria is idiopathic or associated with NAFLD



Limited secondary information is available on the severity and progression of kidney stones for NAFLD-associated hyperoxaluria

Kidney Stones due to NAFLD-associated Hyperoxaluria



Progression

- Progression of NAFLD-associated hyperoxaluria is most characterized by **increased frequency of kidney stones**
- Deposition of **calcium oxalate in kidney tissues (oxalate nephropathy)** can cause tubular-interstitial injury, fibrosis, acute kidney injury, and/or chronic kidney disease¹



Prognosis

- If left undiagnosed/untreated, **hyperoxaluria may lead to kidney damage and death in general**
- **Systemic oxalosis is less common in secondary hyperoxaluria** such as NAFLD-associated hyperoxaluria²

There is little consensus among physicians on how kidney stone recurrence is defined, with most of them relying on their clinical experience



In general, **opinion-leader physicians have less knowledge about recurrence** as it relates to patients with NAFLD-associated hyperoxaluria because there is **lack of progression data/natural history on these conditions**

Physicians are split on their definition of 'recurrence'

N=3 physicians define it as **multiple stones, or increase in size of existing stones occurring within a 2-year window** from the previous kidney stone

"There is no set criteria really for how we're defining this. It could be multiple stones within a 6-month period, or a stone increasing in size over a 2-year period. Really depends on the patient" -UK physician

N=3 physicians (US) defines it as **having had more than one kidney stone at any point in the patient's lifetime**

How do physicians stratify their patients based on stone recurrence?



There is **no standardized way of segmenting/stratifying patients** – physicians only rely on their **personal clinical experience** to do this:

Mild Patients

- **<2 stones per year**
- GFR is 60 and above for most patients (*normal functioning*)
- Rarely require surgery

NOTE: There is a broader base population of mild patients with these conditions whom the physicians do not manage/receive as referrals

Moderate Patients

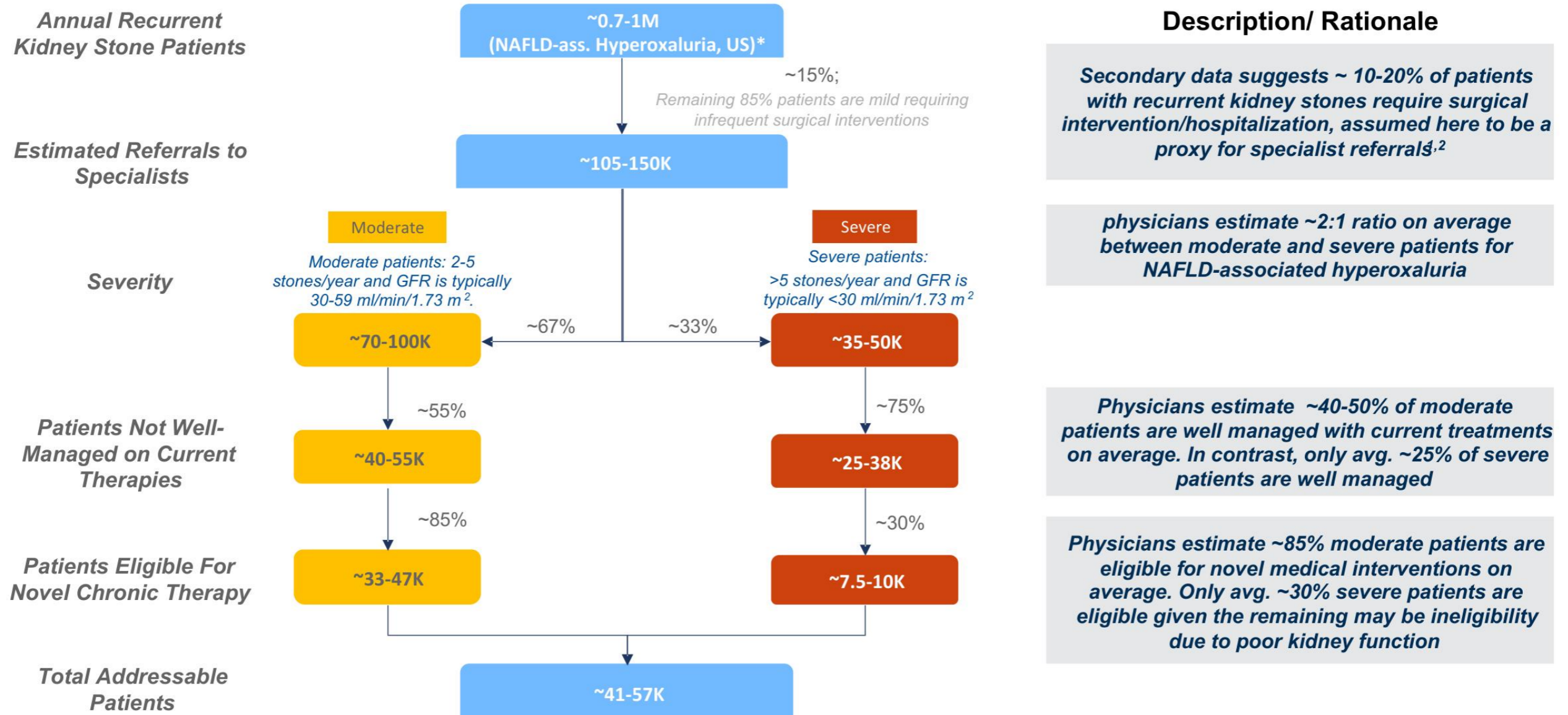
- **2-5 stones per year**
- GFR is 30-59 for most patients (*modest decline in kidney function*)
- Require ~1 surgical intervention per year

Severe Patients

- **>5 stones per year**
- GFR is <30 for most patients, only a fraction remain eligible for new therapies (*severe decline in kidney function*)
- Require 2-3 surgical intervention per year

NOTE: physicians caveat that their managed patient population tends to skew towards more severe patients, as that is when patients are typically referred to them

In the US ~41-57K patients with >2 recurrent kidney stones per year due to hyperoxaluria would be candidates for a novel chronic therapy



*See appendix f for estimate of 0.7-1.0 million recurrent kidney stone patients, other sources in notes

Estimated cost for kidney stone treatments

Treatment:	Pyridoxine (Vitamin B-6)	Alpha Blocker (tamsulosin)	Potassium Citrate	Thiazide Diuretics (hydrochlorothiazide)	Extracorporeal Shock Wave Lithotripsy (ESWL)	Ureteroscope
Estimated Cost:	\$285.00 per year	< \$50 per year			~\$5-15k ¹	\$2,600 ²

The recommended dose of Pyridoxine for patients with kidney stones is **50 MG daily**

The recommended dose of tamsulosin for kidney stones is **0.4 MG daily** until successful expulsion (average 1-2 weeks)

The recommended dose of potassium citrate for kidney stones is **between 30-60 MG daily, and up to 100 MG in some cases**

The recommended dose of thiazide diuretics such as hydrochlorothiazide for kidney stones is **25 to 100 MG daily**

Price ranges for surgical interventions are **dependent** on the **severity** of the kidney stone event; **kidney stone removal** interventions are used when **SoC therapies do not work**, **Kidney transplants and dialysis** are reserved for **very severe** patients that experience a **loss in kidney function**, making them **ineligible** for most trials and new therapies

Group Discussion

UNMET NEED

- What is your perception of the general unmet need for hyperoxaluria patients?
 - Which type of patients do you view as having the greatest unmet need? What type of unmet need?
- Do (or how do) you/your plan define “recurrent stone formation” (RSF) and severity? Do you consider GFR levels or number of kidney stones per year? Or the number of surgical interventions?
 - What do you see as challenges in identifying RSF patients? What criteria may/will you use?
 - Would a biomarker that could potentially indicate severity be valuable beyond what is listed above? What evidence would be needed to establish confidence in such a biomarker?
- What is your perception of the current standard of care for RSF in terms of provider awareness? Efficacy? Cost to plan?
- Which RSF patients do you believe are most suited for a novel therapy?
- What goals would you hope to achieve through treating these patients with a novel therapy?

Please tell us what you think: Polling

- Poll #8
- Poll #9
- Poll #10

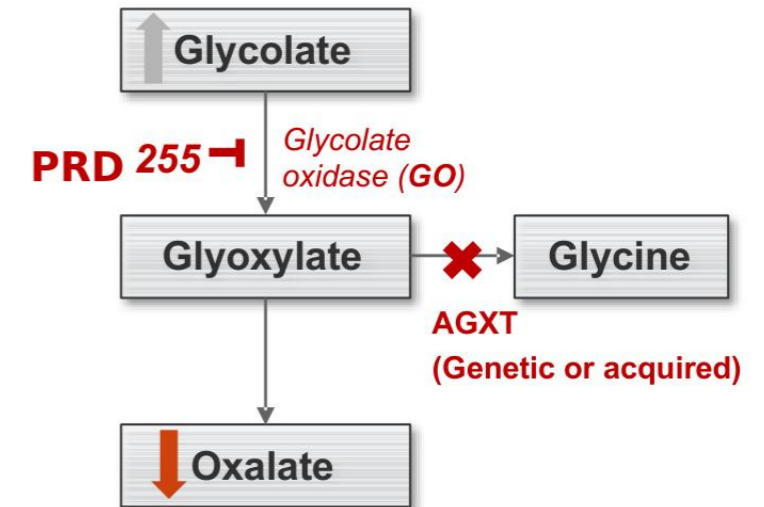
PRD 255 MOA, Target, and Therapeutic Goals

Therapeutic principle

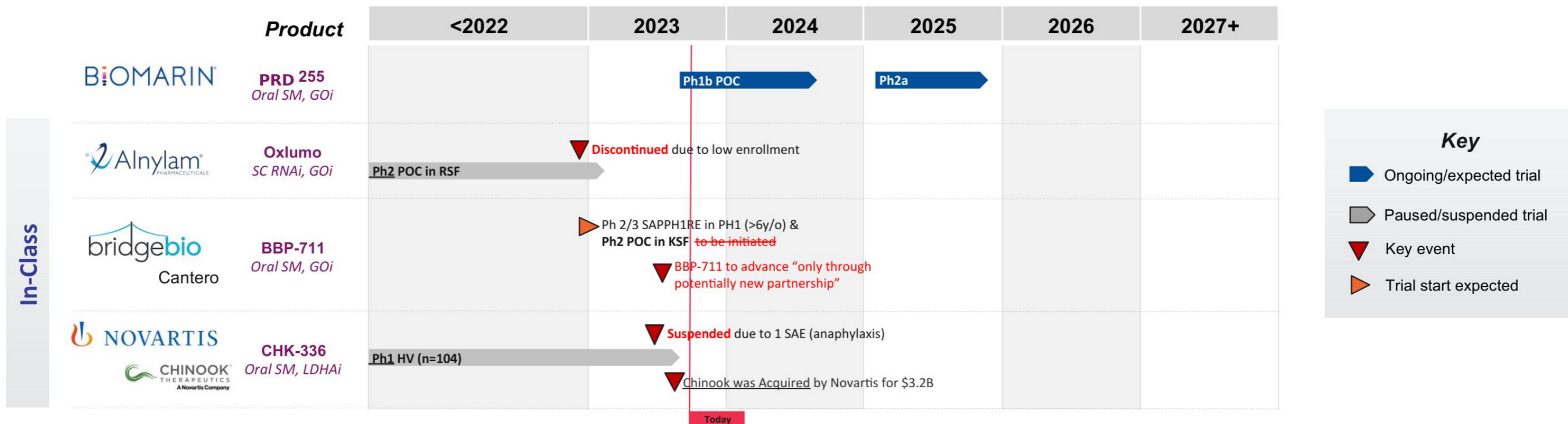
- **PRD 255**: Small molecule, oral GO inhibitor, reducing glyoxalate
 - Lower glyoxylate reduces oxalate
 - Lower urine oxalate reduces renal injury, oxalate burden and stone events

Therapeutic goals

- Reduce/Normalize urine oxalate
- Reduce nephrocalcinosis
- Reduce systemic oxalosis, where present
- **Reduce stone events**
 - e.g., Pain, infection, bleeding, hospitalizations, need for stone removal procedures (e.g., lithotripsy, surgery)
- Prevent decline in eGFR
 - AKI, CKD, ESRD



RSF Pipeline landscape



Potential pivotal study design

<p>Patient Inclusion/Exclusion Criteria</p>	<ul style="list-style-type: none"> • Inclusion Criteria: Adult patients with higher urinary oxalate levels at baseline 2 or more stone events per year (“moderate and severe patients) • Exclusion Criteria: Patients with GFR<30 mg/ml/1.73m² (significant decline in kidney functioning), imminent liver transplant patients
<p>Trial Design</p>	<ul style="list-style-type: none"> • A randomized controlled trial <ul style="list-style-type: none"> – <i>Arm 1:</i> New Agent (oral, once daily) + standard of care (dietary interventions along with supplements) – <i>Arm 2 (comparator): placebo</i> + standard of care (dietary interventions along with supplements)
<p>Efficacy and Endpoints</p>	<ul style="list-style-type: none"> • Primary Endpoints <ul style="list-style-type: none"> – Reduction in urinary oxalate level vs. comparator arm – Reduction in kidney stone recurrence • Secondary Endpoints <ul style="list-style-type: none"> – Patient reported outcomes – QoL improvement – Reduction in rates of hospitalization due to recurrence of kidney stones – Reduction in complication rate such as vascular calcification, cardiovascular event rate – Improvements in radiological imaging
<p>Safety/Tolerability</p>	<ul style="list-style-type: none"> • No significant impact on kidney functioning (as measured by GFR)

Hypothetical PRD 255 Trial Outcome Scenarios

	SCENARIO 1 KS & URINE OX DATA ONLY	SCENARIO 2 + QoL DATA	SCENARIO 3 + SURGERY OFFSET DATA
TARGET PATIENT POPULATION	<ul style="list-style-type: none"> Moderate-to-severe NAFLD-associated hyperoxaluria patients with ≥ 2-5 kidney stones per year and ≥ 1 surgical intervention per year 		
TRIAL DESIGN	<ul style="list-style-type: none"> PRD 255 vs. placebo + physician's choice of treatment (i.e., dietary interventions along with supplements) 		
EFFICACY DATA <i>Change from Scenario 1</i>	<ul style="list-style-type: none"> ~25% Reduction of urine oxalate levels vs. physician's choice ~30-40% Reduction of kidney stone incidence (over 3 years) vs. physician's choice 		
	<ul style="list-style-type: none"> Additional evidence required: A strong link between oxalate levels and stone recurrence / morbidities 	<ul style="list-style-type: none"> $\geq 15\%$ Improvement in QoL, particularly on the pain domain (e.g., EQ5D) 	<ul style="list-style-type: none"> $\geq 15\%$ Improvement in QoL, particularly on the pain domain (e.g., EQ5D) ~30-40% Reduction of surgical interventions to remove kidney stones
COST COMPARATORS	<ul style="list-style-type: none"> Current 2L treatments (i.e., OTC vitamin B-6 & potassium citrate, generic alpha blockers and diuretics) 		<ul style="list-style-type: none"> Kidney stone removal surgical interventions (i.e., ESWL, Anatomic Nephrolithotomy, Ureteroscopy)
Other Evidence	<ul style="list-style-type: none"> Historical cohort data on surgical outcomes in target population to model surgical intervention offset via ITC 		

Breakout Groups

Each group will discuss all questions and report back to larger group

Small Group Discussion: 40 minutes

Report Back: 30 minutes

Group A

Felicia Wade, MD
Kenneth Schaecher, MD
James Bowerman, MD
Joe Biskupiak, PhD
Lynne Milgram, MD
Heather Ollison
Thomas Morgan
Paul Okhuoya
Corinne Cusamano
Cindy Chen
Samuel Amadi PharmD

Group B

Lon Castle, MD
John Fox, MD
Lou Garrison, PhD
Marc Dinnel, PharmD
Ed Pezalla, MD
Joost Van Backle
PJ Keith
Carolina Amador
John Nelson
Lee Blansett
Taylor Crutison

Breakout Group Discussion Points

CLINICAL DEVELOPMENT & ENDPOINTS

- Do you believe a head-to-head trial design (**PRD255** vs placebo + standard care of choice) is compelling? What is your view on the comparators in the design?
- Are the endpoints proposed in Scenario 1 sufficient to demonstrate clinical value of new therapy?
 - What is your perception of urine oxalate (as endpoint) and its linkage to recurrent stone formation?
 - What about absolute vs. relative clinical improvements as endpoints? Is the proposed reduction compelling?
- Does the addition of QoL improvement in Scenario 2 increase the strength of clinical value?
- Does the potential reduction in surgical interventions in Scenario 3 increase the strength of clinical value?
- What are the strengths of the pivotal trial design? What are potential gaps?
- Is there value to an indirect treatment comparison vs. surgery in scenarios 1 or 2?

VALUE PROPOSITION

- What is your perception of the cost comparators proposed in Scenario 1 and 2? In Scenario 3?
- Are there other useful clinical or economic data that will be important to determine value and coverage of **PRD 255**?
- Are there any other disease areas/treatments that may serve as analog for the development of **PRD 255**?

Breakout Groups

Each group will discuss all questions and report back to larger group

Small Group Discussion: 40 minutes

Report Back: 30 minutes

Group A

Group B

Please tell us what you think: Polling

- Poll #11
- Poll #12
- Poll #13
- Poll #15
- Poll #16
- Poll #17

Final Large Group Discussion

COVERAGE POTENTIAL

- How do you anticipate your plan will cover **PRD** 255 and why?
- What factors will be most influential in determining your coverage of **PRD** 255?
- What is your view on the value of **PRD** 255 vs comparators? How do you view the potential cost offsets derived from **PRD** 255? Are there any pricing analogs that come to mind?

Please tell us what you think: Polling

- Poll #18
- Poll #19
- Poll #20



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RECAP & FEEDBACK



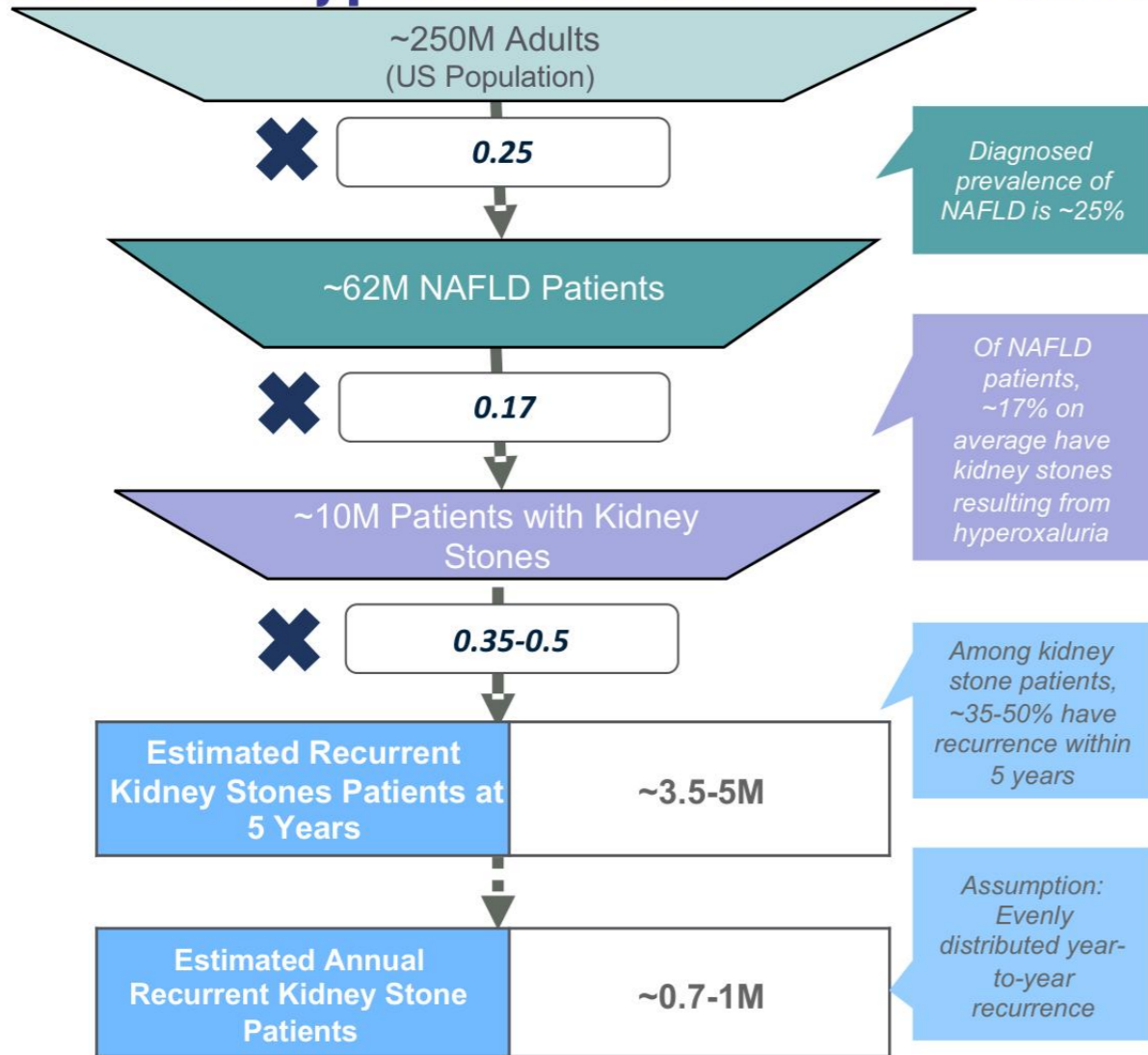
THANK YOU



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APPENDIX

We estimate ~0.7-1M adult patients with recurrent kidney stones due to NAFLD-associated hyperoxaluria in the US annually



Methodology	
Source	Finding
Zhang (2021) ¹	<ul style="list-style-type: none"> 4,024 individuals aged ≥ 20 years were included in the analysis NAFLD prevalence was ~12.4% defined by elevated liver enzymes <ul style="list-style-type: none"> The sensitivity of liver enzyme detection is low since up to ~78% NAFLD patients fall within the normal range
Younossi (2016) ²	<ul style="list-style-type: none"> A global meta-analysis with 8,515,431 adult patients from 22 countries (>94% from US) NAFLD prevalence in US adults is 24.13% Global prevalence of NAFLD is 25.24%
Nam (2016) ³	<ul style="list-style-type: none"> Of 1,381 cases in Korea, the frequency of renal stone disease in the fatty liver patient group was 27%. In contrast, only 8% was noted as renal stone disease in non-fatty liver patient group diagnosed by abdomen-pelvis CT
Wei (2018) ⁴	<ul style="list-style-type: none"> Of 3,719 men enrolled in China, the percentage of NAFLD patients with kidney stones was 8.4% significantly higher than that among patients without NAFLD (6.4%) diagnosed by ultrasonography The percentage of kidney stones in mild, moderate, and severe NAFLD patients is 14%, 12%, and 6%, respectively
Uribarri (1989) ⁵	<ul style="list-style-type: none"> "Natural cumulative recurrence rate of renal stones" was 14% at 1 year, 35% at 5 years, and 52% at 10 years
Ferraro (2017) ⁶	<ul style="list-style-type: none"> Literature review of 21 RCTs with 2,168 participants in 46 study arms over a median follow-up of 3.2 years The cumulative risk of recurrence at 5 years was estimated to be about 53% The median recurrence was 26 per 100 person-years for those undergoing no treatment Recurrence was higher in those untreated or treated with dietary changes compared to those treated with drugs (26 vs. 23 vs. 9 per 100 person-years)

KOL insights indicate the potential to target moderate-to-severe patients that have 2-5+ kidney stones per year

		MILD PATIENTS	MODERATE PATIENTS	SEVERE PATIENTS
Segment Size	Idiopathic	85%	9%	6%
	NAFLD-Associated	85%	10%	5%
Lifetime stone recurrence		<5 stones	5-10 stones	>10 stones
1-year stone recurrence		<2 stones per year	2-5 stones per year	>5 stones per year
Number of surgical procedures required/year		Rarely required	~1 surgical intervention per year (~10% of moderate patients require more than 1 per year)	2-3 surgical interventions per year (~40% of severe patients require more than 3 per year)
<p><i>Trial Design Required for P&MA Success</i></p>		<ul style="list-style-type: none"> • H2H trial vs. physicians' choice of treatment • Demonstrated H2H superiority in the reduction of kidney stones that require surgical intervention • Trial inclusion criteria that specify the inclusion of patients with ≥ 2-5 kidney stones per year and ≥ 1 surgical intervention per year • Trial exclusion criteria that excludes patients with severely impaired kidney function (i.e., require transplant or dialysis) 		

Group Discussion: Value Proposition of Gene Therapy

Advantages?

Challenges?