# 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 BioMarin attendees but 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, BMN 255, and expected payer coverage across various potential development scenarios.

BMN 255 is an investigational gene therapy. It has not been approved and has not been determined to be safe or effective.

# 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 |
| **Kenneth Schaecher, MD** | University of Utah Health Plan |
| **Lon Castle, MD** | Express Scripts \| EviCore |
| **Lou Garrison, PhD** | University of Washington School of Pharmacy |
| **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 |
| **Jolene Lau** | Director, Corporate Intelligence |
| **Paul Okhuoya** | Director, Global Market Access Lead, BMN 255 |
| **Thomas Morgan** | Medical Director, Early Discovery Medicine, BMN 255 |
| **Carolina Amador** | Associate Director, Corporate Intelligence, BMN 255 |

| FACILITATORS | ORGANIZATION |
|---|---|
| **Lee Blansett** | HMP Market Access Insights **(MODERATOR)** |
| **Cindy Chen** | HMP Market Access Insights |
| **Taylor Crutison** | HMP Market Access Insights |
| **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 BMN Development/Pipeline** |
| 11:20-1:20 | Johnny Chew/<br>Jolene Lau | **Gene Therapy: Perception, Management and Planning for the future**<br>• Current and pipeline landscape<br>• Management of gene therapy<br>• Value perception |
| 1:20-1:40 | | **Break** |
| 1:40-3:45 | Thomas Morgan/<br>Carolina Amador | **BMN 255: Non-Alcoholic Fatty Liver Disease (NAFLD)-associated Hyperoxaluria**<br>• Disease background<br>• Unmet need (therapeutic landscape)<br>• Development plan: product profile, trial design and endpoints<br>  • Large group discussion<br>  • Break out group discussion |
| 3:45-4:00 | Lee Blansett | **Meeting recap, advisor feedback for 2023** |

# BMN 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

Source: https://www.biomarin.com/our-treatments/pipeline/

AAV: adeno-associated virus; DMD: Duchenne Muscular Dystrophy; HAE: hereditary angioedemaHCM: hypertrophic cardiomyopathy

# US STRATEGIC COUNCIL FOR DEMONSTRATING EFFECTIVENESS

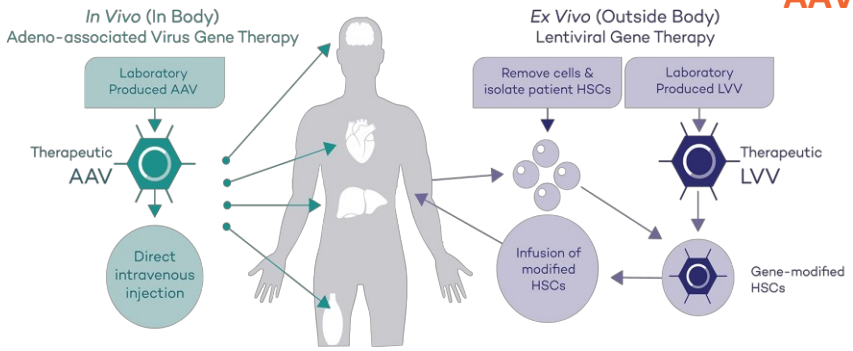
## GENE THERAPY

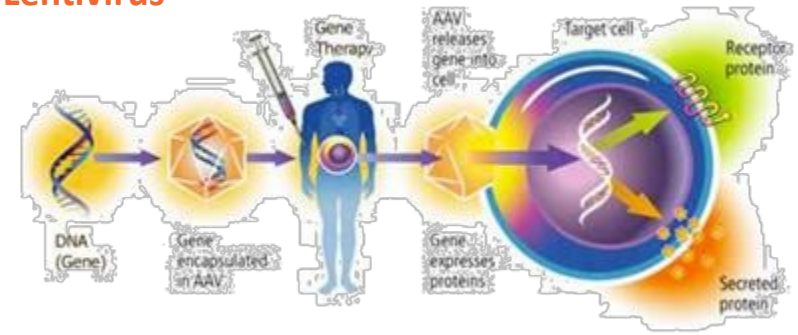
# Gene Therapy Platforms

## Gene Therapy Platforms

### Gene replacement (viral vectors)

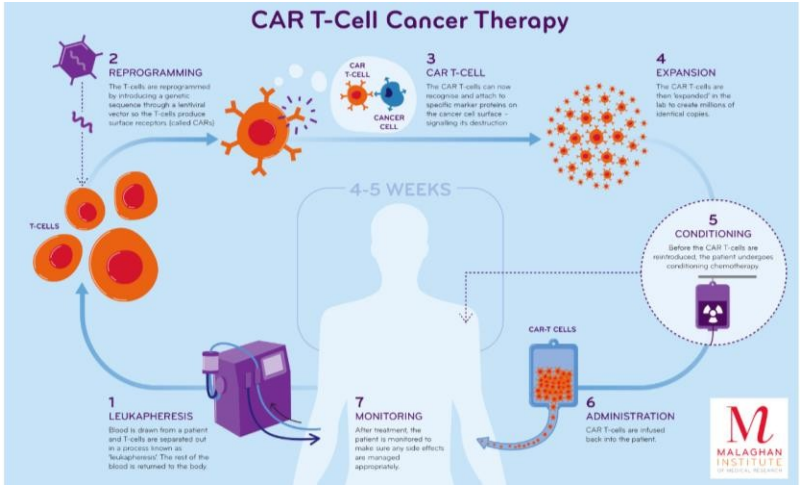
**AAV, Lentivirus**

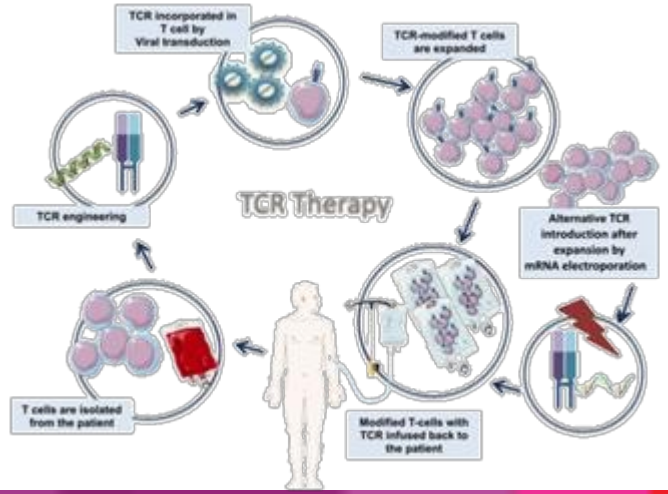



### Genetically modified cell-based immunotherapies

**CAR T cell therapies, TCR therapies, NK cell therapies**



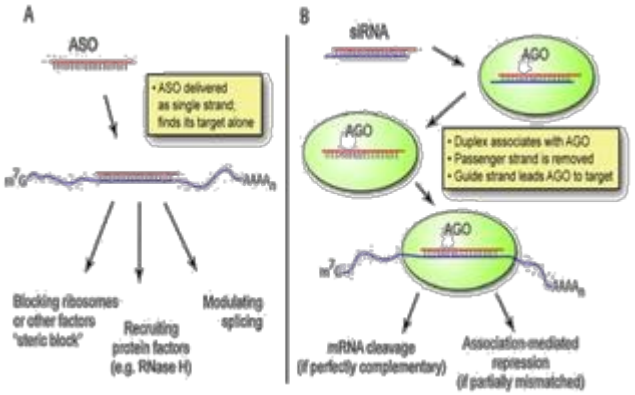

Sources in Notes

# Gene Therapy Platforms

## Gene Therapy Platforms

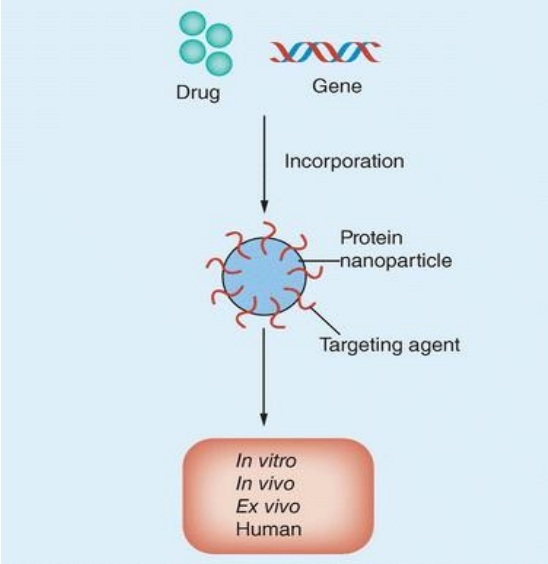
### Gene Silencing

siRNAs, ASOs



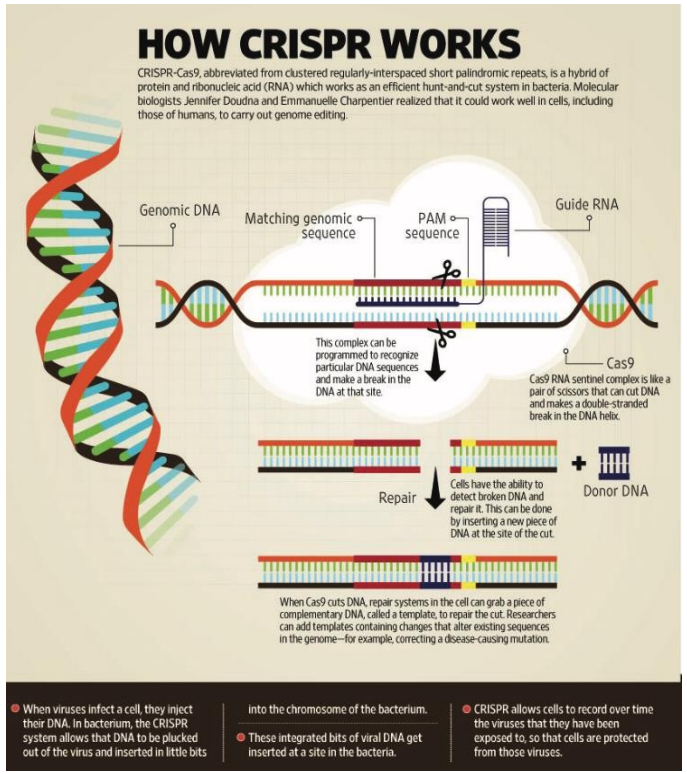

### Non-viral vectors

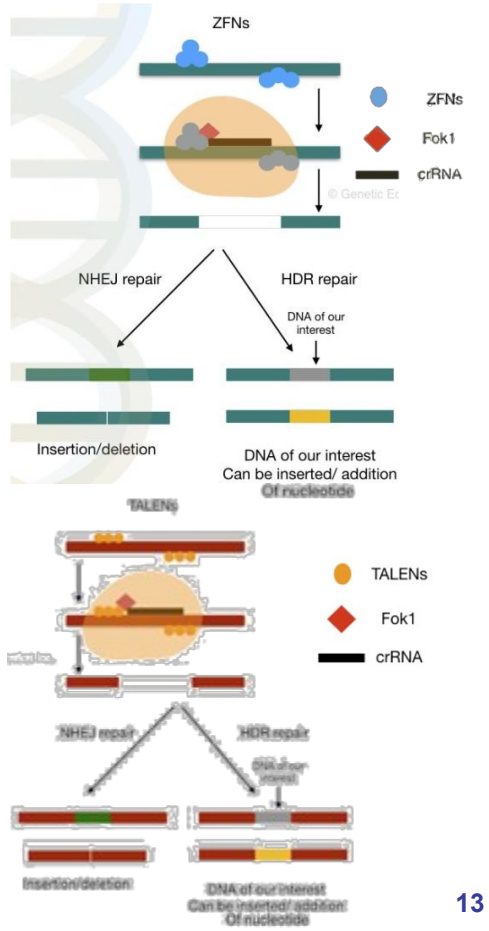
Nanoparticles, Nanospheres




### Gene Editing

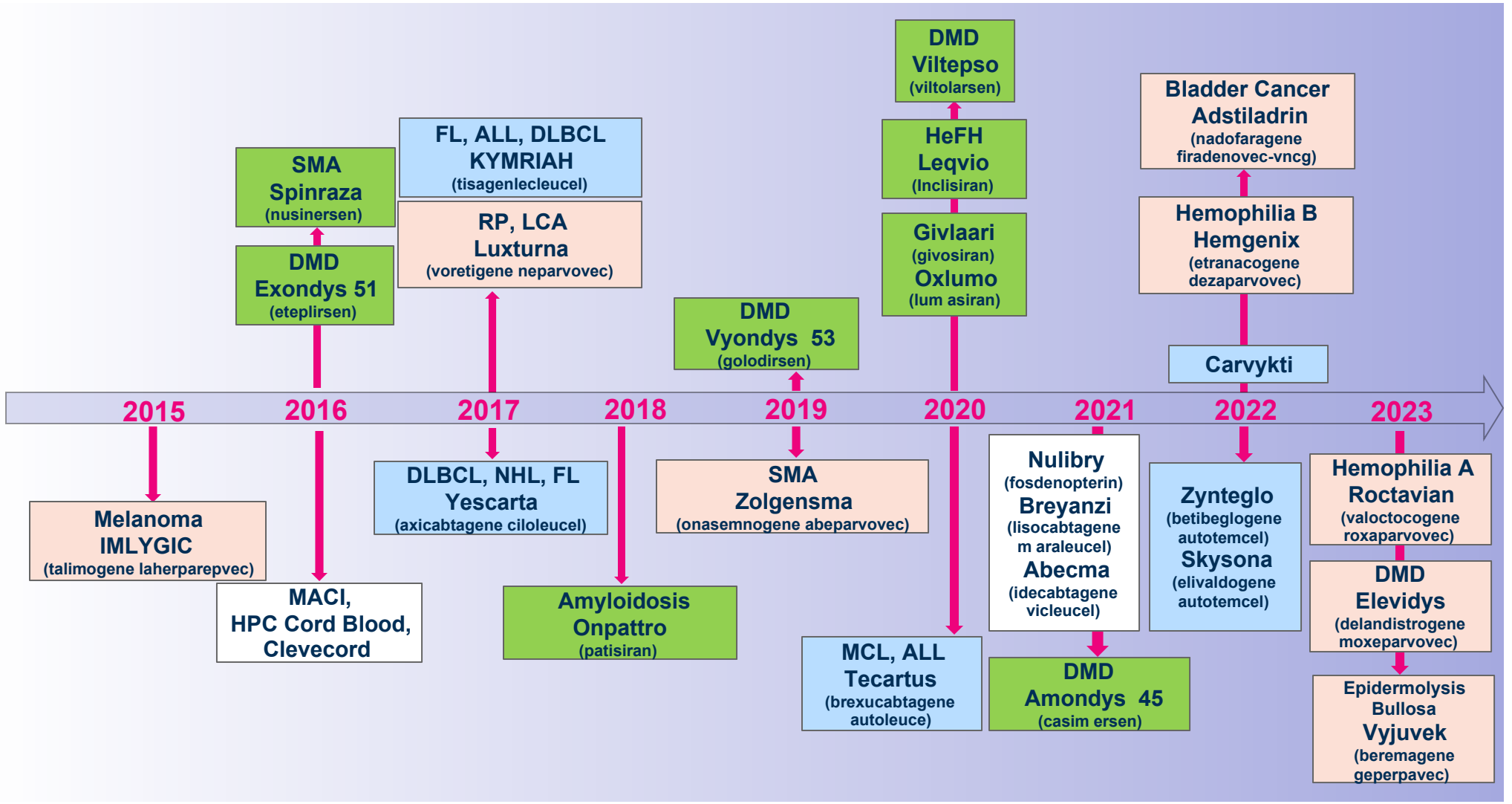
CRISPR/Cas, Zinc finger nucleases, TALENs




Sources in Notes

# 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)

Sources in Notes. Please ref er to the relev ant Prescribing Inf ormation f or f urther inf ormation on the products mentioned here.

# 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**<br>*Tumor responses determined using modified World Health Organization (WHO) criteria by a blinded, independent Endpoint Assessment Committee (EAC)[3,4] | **Study Design** NCT00999609<br>• Phase III, open-label, RCT<br>• N=31 patients, aged 3 or older[1]<br>○ Intervention Arm (n=21): subretinal administration of AAV2-hRPE65v2 (voretigene neparvovec-rzyl)<br>○ Control Arm (n=10): No intervention, uninjected[1]<br>**Primary Endpoint**<br>• Multi-luminance Mobility Testing (MLMT)*, Bilateral (1-year change from baseline)[1]<br>**Secondary Endpoint**<br>• Full-field Light Sensitivity Threshold (FST) Testing: White Light (1-year change from baseline)[1]<br>**Results**<br>• MLMT score change for bilateral eyes, median(min,max)<br>○ Luxturna: 2(0,4)[2]; Control: 0(-1,2)[2]<br>• Luxturna's demonstrated efficacy at 1-year<br>○ 55% of all participants had an MLMT score change of 2 or greater[3]<br>*MLMT is a standardized, lab-based test w here participants were observed navigating an obstacle course of varying height under different levels of illumination[2-4] | **Study Design** NCT03381729<br>• Phase III, open-label, single-arm, single-dose<br>• N=22 patients, aged 6 months or younger[1,2]<br>• Intervention: AVXS-101 delivered intravenously<br>**Primary Endpoints**<br>• Independent sitting for at least 30 seconds (up to 18 months)[1]<br>• Event-free survival (14 months)<br>**Secondary Endpoint**<br>• Ability to thrive (18 months)[1]<br>**Results**<br>• Motor milestone: 59% of patients could sit independently for at least 30 seconds[2]<br>• Event free survival: 91% of patients were alive and did not need permanent breathing support[2]<br>• 64% of patients could sit without support for at least 30 seconds at any point in the study[2*]<br>*One patient sat independently for 30 seconds or more at 16 months of age, but this milestone w as not reconfirmed at the 18 months of age study visit (end of study)[2] | **Study Design** (NCT02773849)<br>• Phase III, open-label, multicenter, single-arm study<br>• N=157 patients, aged 18 or older<br>• Population: high-risk, Bacillus Calmette-Guérin (BCG)-unresponsive non–muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS)[1]<br>• Intervention: Adstiladrin delivered intravesically<br>**Primary Endpoint**<br>• Number of patients with CIS with a complete response (CR) (12 months)[1]<br>**Secondary Endpoint**<br>• Durability of CR in patients with CIS (up to 60 months)[4]<br>**Results**<br>• 51% of the CIS cohort achieved CR, all by 3 months[1]<br>• Duration of response*: 9.7 months (median); % of patients with duration ≥12 months: 46%[1]<br>• During the 12-month study period[2]:<br>○ 96% of patients did not progress to MIBC<br>○ 74% of patients were cystectomy free<br>○ 36% of patients remained free of high-grade recurrence up to 2 years.<br>*Based on patients (n=50) w ho achieved a CR; reflects period from the time CR w as achieved.[1] |
| **Price** | $425K (per eye) one-time treatment | $2.1M WAC | $60k per administration, every 3 months (quoted cash price) |

WAC: Wholesale Acquisition Price; Sources in Notes

# 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** | **Study Design** NCT03569891<br>• Phase III, open-label, single-dose, RCT<br>• N=54 patients[2]<br>• Experimental arm: A single infusion of AAV5-hFIXco-Padua (AMT- 061)[1]<br>• Active comparator:FIX replacement [1]<br>**Primary Endpoint**<br>• Annualized bleeding rate (ABR) [1]<br>**Secondary Endpoint**<br>• Factor IX Activity Levels after AMT-061<br>**Results**<br>• 54% reduction of all bleeds on Hemegenix (average of 4.1 ABR while on factor IX prophylaxis; 1.9 ABR on Hemegenix) [2]<br>• 37% average factor IX sustained increase in 2 years on Hemegenix<br>• 63% reported zero bleeds in the 7 to 18-month period following Hemgenix<br>• 94% of Hemegenix patients remained prophy-free.[2] | **Study Design** NCT04491604<br>• Phase III, intra-subject parallel study<br>• N=31 patients<br>• Experimental arm: Primary wound receives B-VEC<br>• Placebo comparator arm: Primary wound receives placebo<br>**Primary Endpoint**<br>• Primary wound with 100% wound closure on Weeks 22 and 24 or Weeks 24 and 26 [1]<br>**Secondary Endpoint**<br>• Primary wound with 100% wound closure on weeks 8 and 10 or weeks 10 and 12 [1]<br>**Results**<br>• Vyjuvek demonstrated a significantly higher percentage of complete wound healing compared with placebo [2]<br>• Of the wounds treated with Vyjuvek that were closed at 3 months, 67% were also closed at 6 months [3] | **Study Design** Phase 1&2 (SRP-9001) NCT03769116<br>• **Study 1:** Multi-center study including:<br>○ Part 1: 48-week, randomized, double-blind, placebo-controlled period [1]<br>○ Part 2: 48-week period that began following completion of Part 1.[1]<br>• **Study 2:** Open-label, multi-center study with a cohort of 20 ambulatory male DMD subjects aged 4 through 7 years.<br>**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]<br>**Primary Endpoints for Study 2:** Effect of Elevidys micro-dystrophin expression [1]<br>**Results**[1]<br>Mean Elevidys micro-dystrophin expression levels (change from baseline) at Week 12 following infusion for patients 4 to 5 were:<br>• 95.7% (N=3, SD: 17.9%) in Study 1<br>• 51.7% (N=11, SD: 41.0%) in Study 2 | **Study Design** (BMN 270-301) NCT03370913<br>• Phase III, open-label, single-arm study<br>• N=112 patients<br>• Population: Hemophilia A patients With residual FVIII Levels ≤ 1 IU/dL receiving prophylactic FVIII infusions[1]<br>**Primary Endpoint**<br>• Change in FVIII activity post-BMN 270 infusion[3]<br>**Secondary Endpoints**<br>• Change in the annualized utilization of exogenous FVIII replacement [3]<br>• Change in the annualized number of bleeding episodes requiring FVIII replacement treatment[3]<br>**Results**[1,2]<br>Annualized bleeding rate (ABR) and events:<br>• 52% mean ABR reduction post Roctavian (2.6 bleeds/year vs 5.4 bleeds/year baseline) [2]<br>• Roctavian ABR: 0.5 bleeds/year for spontaneous bleeds and 0.6 bleeds/year for joint bleeds<br>• Baseline ABR on FVIII prophylaxis: 2.3 bleeds/year for spontaneous bleeds and 3.1 bleeds/year for joint bleeds [2] |
| 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 |

WAC: Wholesale Acquisition Price; Sources in Notes

# 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 moxeparvovec (SRP-9001) fo 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 |
|---|---|
| Study 1* | • Part 1: a 48-week, randomized, double-blind, placebo-controlled period<br>• 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.<br><br>Patients were randomized to receive either ELEVIDYS (N=20) or placebo (N=21). In the ELEVIDYS group, 8 patients received $1.33 \times 10^{14}$ vg/kg of ELEVIDYS, and 12 patients received lower doses. |
| | **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. |
| Study 2* | 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.<br><br>Subjects received corticosteroids for DMD before infusion. All subjects had baseline anti-AAVrh74 antibodies titers <1:400 and received a single intravenous infusion of $1.33 \times 10^{14}$ vg/kg ELEVIDYS. |
| | **Primary objective:** Evaluate the effect of ELEVIDYS micro-dystrophin expression. |

**% 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 |
|---|---|---|---|
| **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]**

| | ELEVIDYS[e] | Placebo |
|---|---|---|
| **Least squares mean change from baseline (SE) Patients 4-5 yrs** | 4.3 (0.7) n=8 | 1.9 (0.7) n=8 |

**a** Change f rom baseline was statistically significant
**b** All patients receiv ed 1.33 x 1014 v g/kg, as measured by ddPCR
**c** Adjusted f or muscle content. Control was lev el of wild-ty pe (normal) dy strophin in normal muscle
**d** Data are f rom exploratory subgroup analy ses
**e** Demonstrates a numerical adv antage f or ELEVIDYS compared to placebo

Sources: ELEVIDYS [Prescribing inf ormation]. Sarepta Therapeutics, Inc.; 2023; https://classic.clinicaltrials.gov/ct2/show/NC T03769116

# Group Discussion

## PERCEPTION OF ELEVIDYS

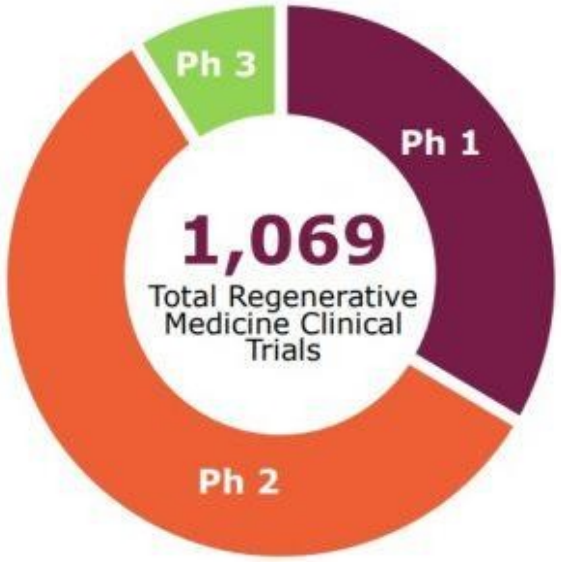
- What is your perception in terms of clinical value based on Elevidys' clinical package?
  - What is your reaction to the change in micro-dystrophin levels? Is there value in the biomarker change?
  - Were the changes in NSAA scores in the approved population compelling in your decision to cover?

- 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 4 $^{th}$ to 6$^{th}$ 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

Alliance for Regenerative Medicine




**Phase 1: 358**
across all tech types and indications

**Gene Therapy:** 117
**Gene-Modified Cell Therapy:** 187
**Cell Therapy:** 49
**Tissue Engineering:** 5

**Phase 2: 617**
across all tech types and indications

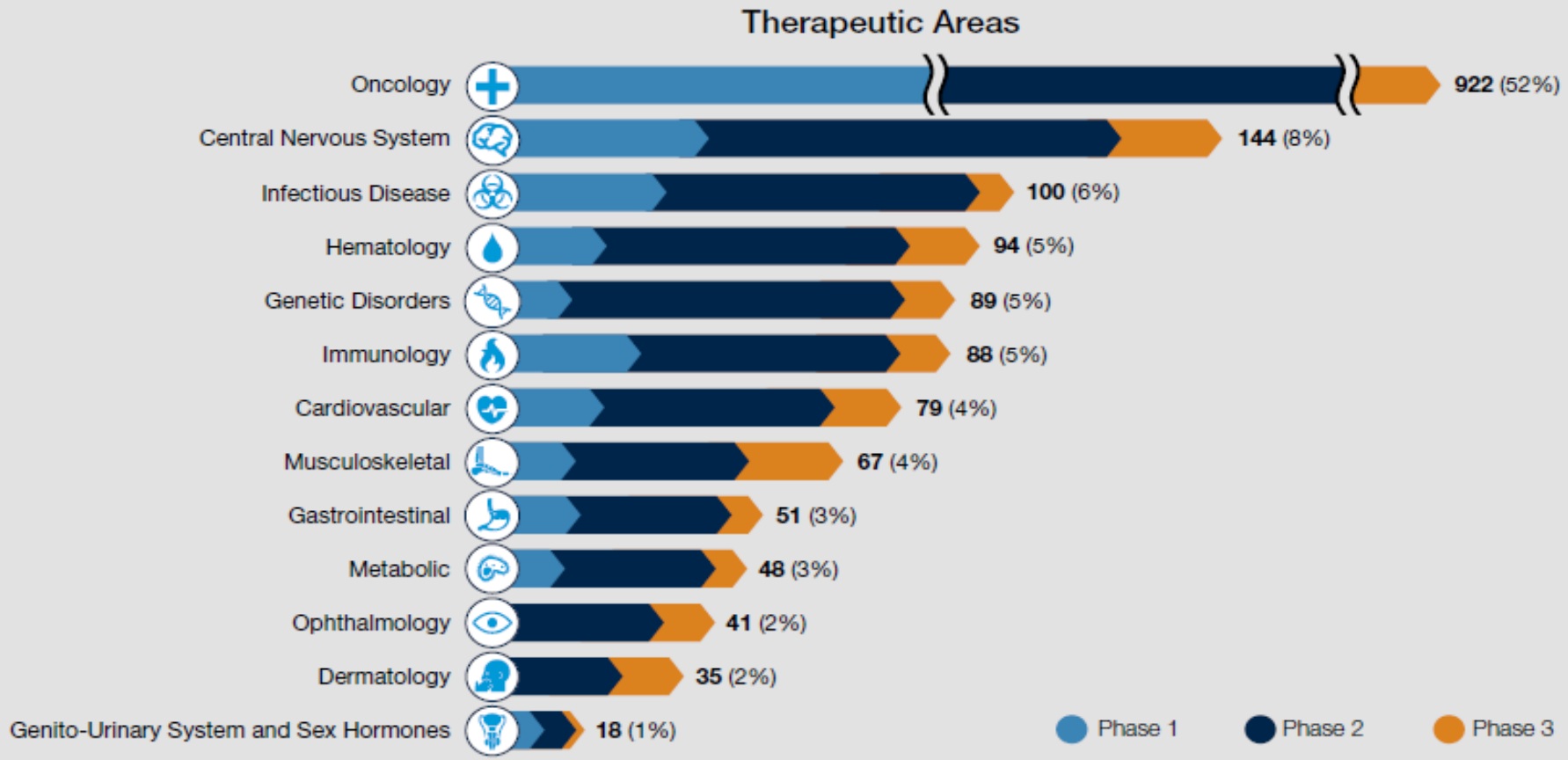
**Gene Therapy:** 219
**Gene-Modified Cell Therapy:** 207
**Cell Therapy:** 168
**Tissue Engineering:** 23

**Phase 3: 94**
across all tech types and indications

**Gene Therapy:** 30
**Gene-Modified Cell Therapy:** 16
**Cell Therapy:** 32
**Tissue Engineering:** 16

Source: Dan S. In the pipeline: Surge of cell and gene therapies likely in 2020. Alliance For Regenerativ e Medicine. Av ailable 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)



Sources in Notes

# Cell and Gene Therapy Pipeline Outlook

BLA/MAA Accepted

| 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 **(Iovance)** | 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 |



Source: https://pay orsolutions.cvshealth.com/sites/default/files/Q32023GeneTherapy PipelineCVSHealthAugust2023.pdf . Source: http://alliancerm.org/wp-content/uploads/2023/08/20230808-Sector-Snapshot_Final_2023.pdf

# Group Discussion

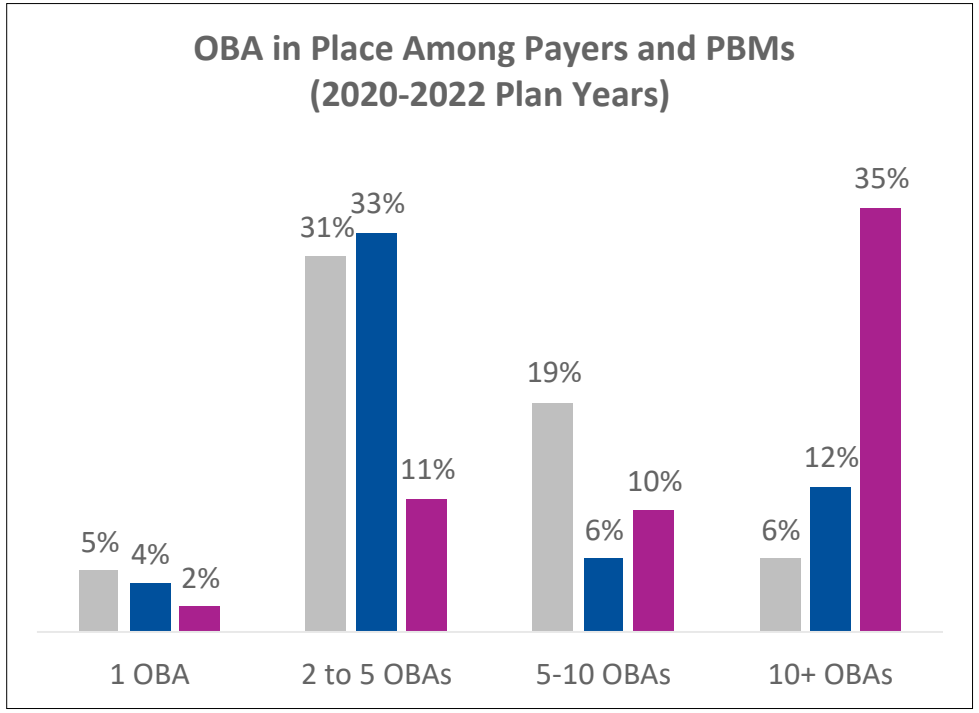
## PLANNING FOR PIPELINE GENE THERAPIES

- 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)**

1. Oncology (17%)
2. Cardiology (12%)
3. Endocrinology (11%)

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8. Rare/Orphan (8%)

**74%**

preferred agreements with both claims-based and clinical outcomes

Percentages used based on sources and calculation of cumulative categories. Source: 1. "Avalere Survey: Over Half of Health P lans Use Outcomes-Based Contracts", Avalere, November 4,2021. https://avalere.com/insights/avalere-survey-over-half-of-health-plans-use-outcomes-based-contracts 2."Survey Finds 58% of Payers Use Outcome-based Contracts", Avalere, April 5, 2023. https://avalere.com/insights/58-of-payers-use-outcomes-based-contracts

# 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



Sources in Notes

# 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

| 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 BioMarin Development/Pipeline** |
| 11:20-1:20 | Johnny Chew/<br>Jolene Lau | **Gene Therapy: Perception, Management and Planning for the future**<br>• Current and pipeline landscape<br>• Management of gene therapy<br>• Value perception |
| 1:20-1:40 | | **Break** |
| 1:40-3:45 | Thomas Morgan/<br>Carolina Amador | **BMN 255: Non-Alcoholic Fatty Liver Disease (NAFLD)-associated Hyperoxaluria**<br>• Disease background<br>• Unmet need (therapeutic landscape)<br>• Development plan: product profile, trial design and endpoints<br>  • Large group discussion<br>  • Break out group discussion |
| 3:45-4:00 | Lee Blansett | **Meeting recap, advisor feedback for 2023** |

# US STRATEGIC COUNCIL FOR DEMONSTRATING EFFECTIVENESS

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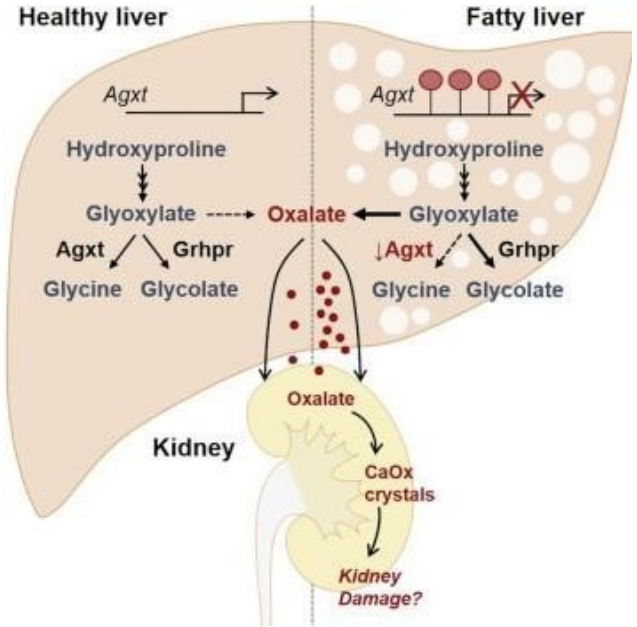
# BMN 255 IN HYPEROXALURIA WITH RECURRENT KIDNEY STONE FORMATION

# 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 levels***[2]

| | |
|---|---|
| **Disease Description** | • Disruption of normal metabolic function in the liver caused by NAFLD leads to excess oxalate accumulation in the urine<br>• 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 urination[1] |
| **Etiology** | • NAFLD-associated hyperoxaluria is caused by excess fat accumulation in the liver<br>– Excess fat accumulation may cause downregulation of Agxt<br>• Downregulation of AGXT diminishes the capacity of the liver to detoxify and remove glyoxylate, causing oxalate accumulation, leading to elevated urinary oxalate levels[2] |

NAFLD: nonalcoholic fatty liver disease

# 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*

**Dietary Modifications**

***Smaller stones*** *(i.e., <1cm) are often* ***treated with just a combination of dietary interventions*** *(particularly higher intake of fluids to let the stones pass naturally) and* ***OTC pain medication***

Modifications to the patients' diet are a primary intervention. These include:

- **Increasing fluid intake**
- **Reducing oxalate intake** (limit salt, avoid grapefruit juice, etc.)
- **Increasing calcium consumption**
- **Avoiding excess vitamin C supplement**

**Supplemental Medications**

***Conservative treatments are effective in controlling:***

- *Nearly all mild patients*
- *40-50% of moderate patients*
- *25% of severe patients (typically require surgery)*

*To reduce oxalate levels,*

- **Pyridoxine (Vitamin B-6)**

*To prevent buildup of calcium oxalate crystals from forming,*

- **Oral potassium citrate**
- **Pyrophosphates**

*For stone prevention/chemolysis,*

- **Thiazide Diuretics**

*For pain and infection associated with kidney stones,*

- **NSAIDs**
- **Alpha blockers**
- **Antibiotics**

**Additional Interventions**

*N=1 mentioned the risk of developing vascular calcifications in frequent stone formers*

*Surgical removal of larger kidney stones (1-2cm in size)*

- **Extracorporeal Shock Wave Lithotripsy (ESWL)**
- **Anatrophic nephrolithotomy**
- **Ureteroscope**

*Organ transplants as a treatment option only occur for the most severe cases and may serve as a cure; although this is rarely performed*

***<25%*** *of the* ***moderate-severe patients with recurrent kidney stones due to NAFLD-associated and idiopathic hyperoxaluria*** *might develop additional complications such as* ***CKD and progress to ESRD over a ~20-year period***

*Source: Primary Market Research, May 2022*

# 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 disease[1]

**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 hyperoxaluria[2]

Sources in Notes

# 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

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

*"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*

## 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

### 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

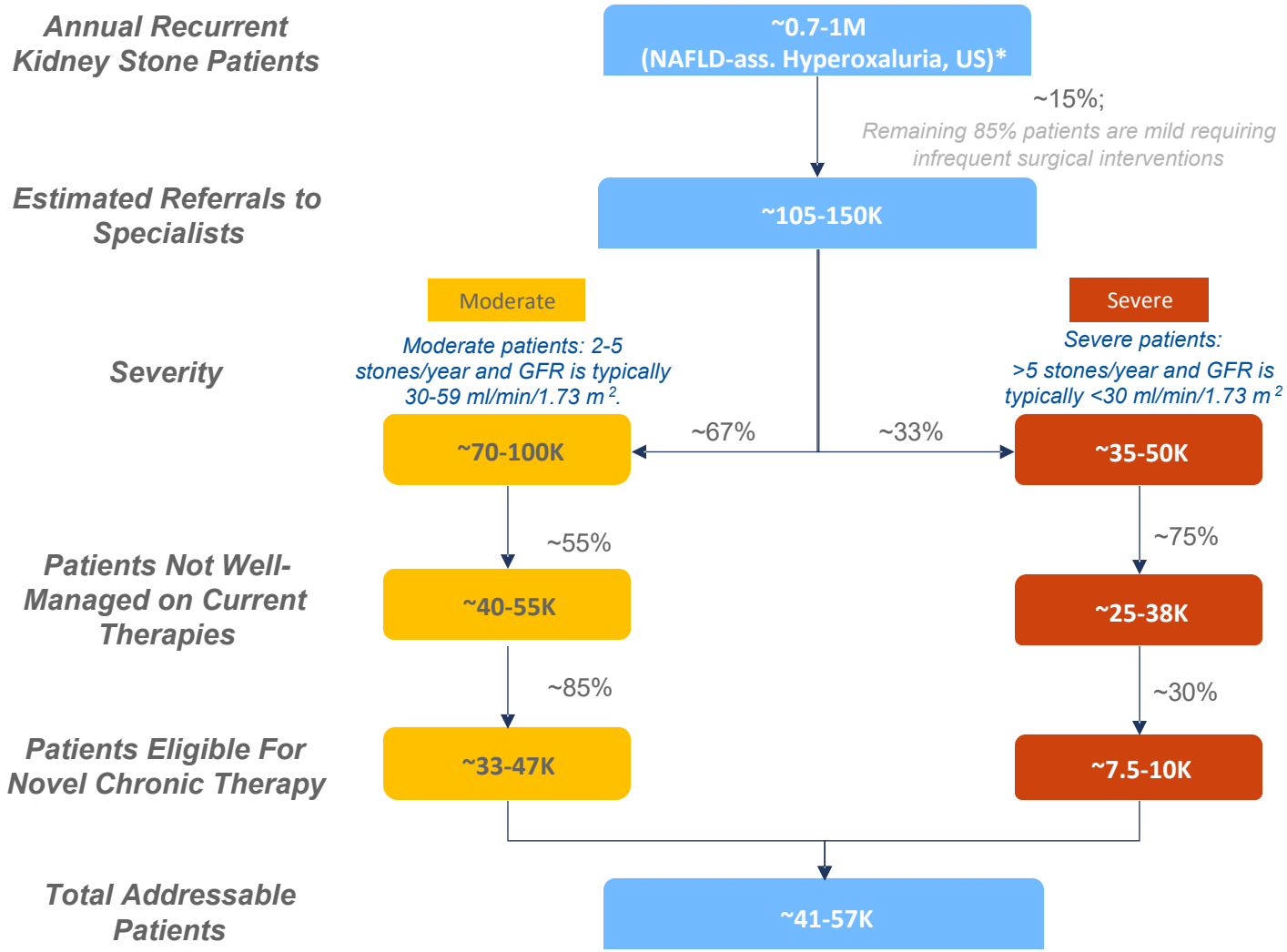
- **>5 stones per year**
- GFR is <30 for most patients, only a fraction remain eligible for new therapies *(severe decline in kidney function)*
- Require 2-3 surgical intervention per year

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

***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***

Source: BMRN Market Research, GFR: glomerular filtration rate (kidney function test)

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




## Description/ Rationale

***Secondary data suggests ~ 10-20% of patients with recurrent kidney stones require surgical intervention/hospitalization, assumed here to be a proxy for specialist referrals[1,2]***

***physicians estimate ~2:1 ratio on average between moderate and severe patients for NAFLD-associated hyperoxaluria***

***Physicians estimate ~40-50% of moderate patients are well managed with current treatments on average. In contrast, only avg. ~25% of severe patients are well managed***

***Physicians estimate ~85% moderate patients are eligible for novel medical interventions on average. Only avg. ~30% severe patients are eligible given the remaining may be ineligibility due to poor kidney function***

*See appendix f or 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

Sources: pricing analysis and secondary market research, additional sources in notes, please relevant PIs for further information

# 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

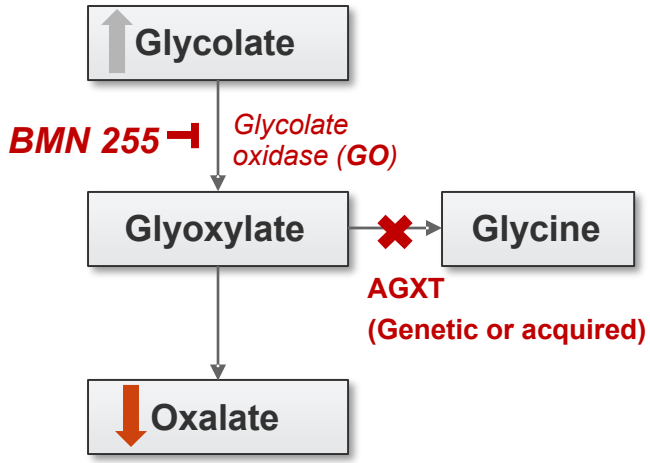
# BMN 255 MOA, Target, and Therapeutic Goals

## Therapeutic principle

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

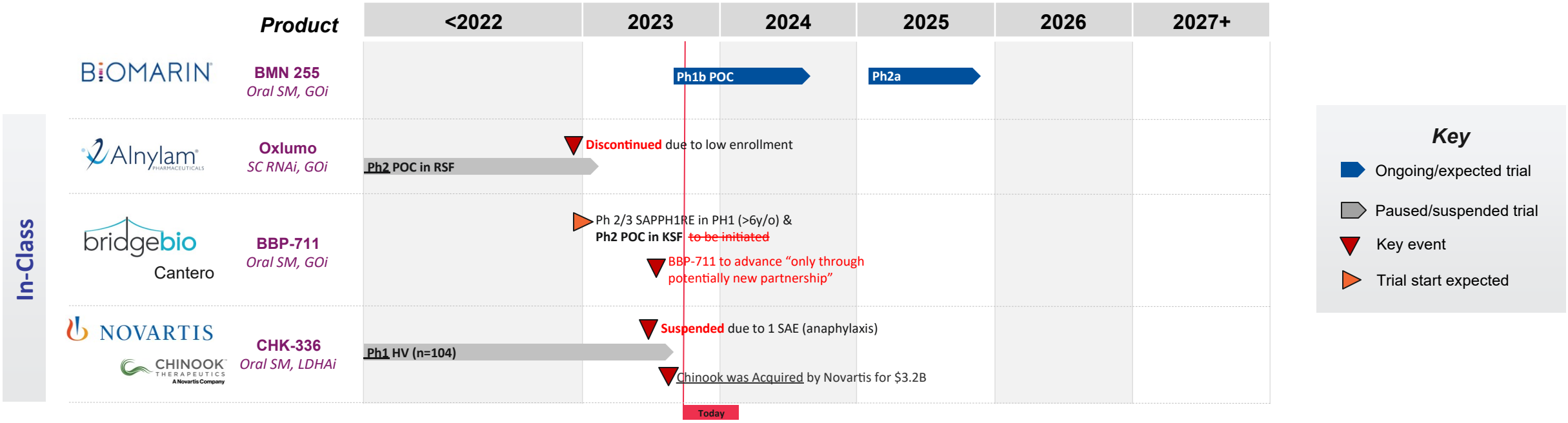
## Therapeutic goals

- 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




Based on BMRN analy sis

# RSF Pipeline landscape




RSF: Recurrent Stone Formation

# Potential pivotal study design

| | |
|---|---|
| ***Patient Inclusion/Exclusion Criteria*** | • **Inclusion Criteria**: Adult patients with higher urinary oxalate levels at baseline 2 or more stone events per year ("moderate and severe patients)<br>• **Exclusion Criteria:** Patients with GFR<30 mg/ml/1.73m$^2$ (significant decline in kidney functioning), imminent liver transplant patients |
| ***Trial Design*** | • **A randomized controlled trial**<br>− *Arm 1:* New Agent (oral, once daily) + standard of care (dietary interventions along with supplements)<br>− *Arm 2 (comparator): placebo* + standard of care (dietary interventions along with supplements) |
| ***Efficacy and Endpoints*** | • **Primary Endpoints**<br>− Reduction in urinary oxalate level vs. comparator arm<br>− Reduction in kidney stone recurrence<br>• **Secondary Endpoints**<br>− Patient reported outcomes<br>− QoL improvement<br>− Reduction in rates of hospitalization due to recurrence of kidney stones<br>− Reduction in complication rate such as vascular calcification, cardiovascular event rate<br>− Improvements in radiological imaging |
| ***Safety/ Tolerability*** | • No significant impact on kidney functioning<br>*(as measured by GFR)* |

# Hypothetical BMN 255 Trial Outcome Scenarios

| | SCENARIO 1<br>KS & URINE OX DATA ONLY | SCENARIO 2<br>+ QoL DATA | SCENARIO 3<br>+ SURGERY OFFSET DATA |
|---|---|---|---|
| **TARGET PATIENT POPULATION** | • Moderate-to-severe NAFLD-associated hyperoxaluria patients with ≥2-5 kidney stones per year and ≥1 surgical intervention per year | | |
| **TRIAL DESIGN** | • BMN 255 vs. placebo + physician's choice of treatment (i.e., dietary interventions along with supplements) | | |
| **EFFICACY DATA**<br>***Change from Scenario 1*** | • ~25% Reduction of urine oxalate levels vs. physician's choice<br>• ~30-40% Reduction of kidney stone incidence (over 3 years) vs. physician's choice | | |
| | • Additional evidence required: A strong link between oxalate levels and stone recurrence / morbidities | • ***≥ 15% Improvement in QoL, particularly on the pain domain (e.g., EQ5D)*** | • ***≥ 15% Improvement in QoL, particularly on the pain domain (e.g., EQ5D)***<br>• ***~30-40% Reduction of surgical interventions to remove kidney stones*** |
| **COST COMPARATORS** | • Current 2L treatments (i.e., OTC vitamin B-6 & potassium citrate, generic alpha blockers and diuretics) | | • Kidney stone removal surgical interventions (i.e., ESWL, Anatrophic Nephrolithotomy, Ureteroscope) |
| **Other Evidence** | • 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 (BMN255 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 BMN 255?
- Are there any other disease areas/treatments that may serve as analog for the development of BMN 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 BMN 255 and why?
- What factors will be most influential  in determining  your coverage of BMN 255?
- What is your view on the value of BMN 255 vs comparators? How do you view the potential cost offsets derived from BMN 255? Are there any pricing analogs that come to mind?

# Please tell us what you think: Polling

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



MMRC-AATD349-00005 0922

# US STRATEGIC COUNCIL FOR DEMONSTRATING EFFECTIVENESS

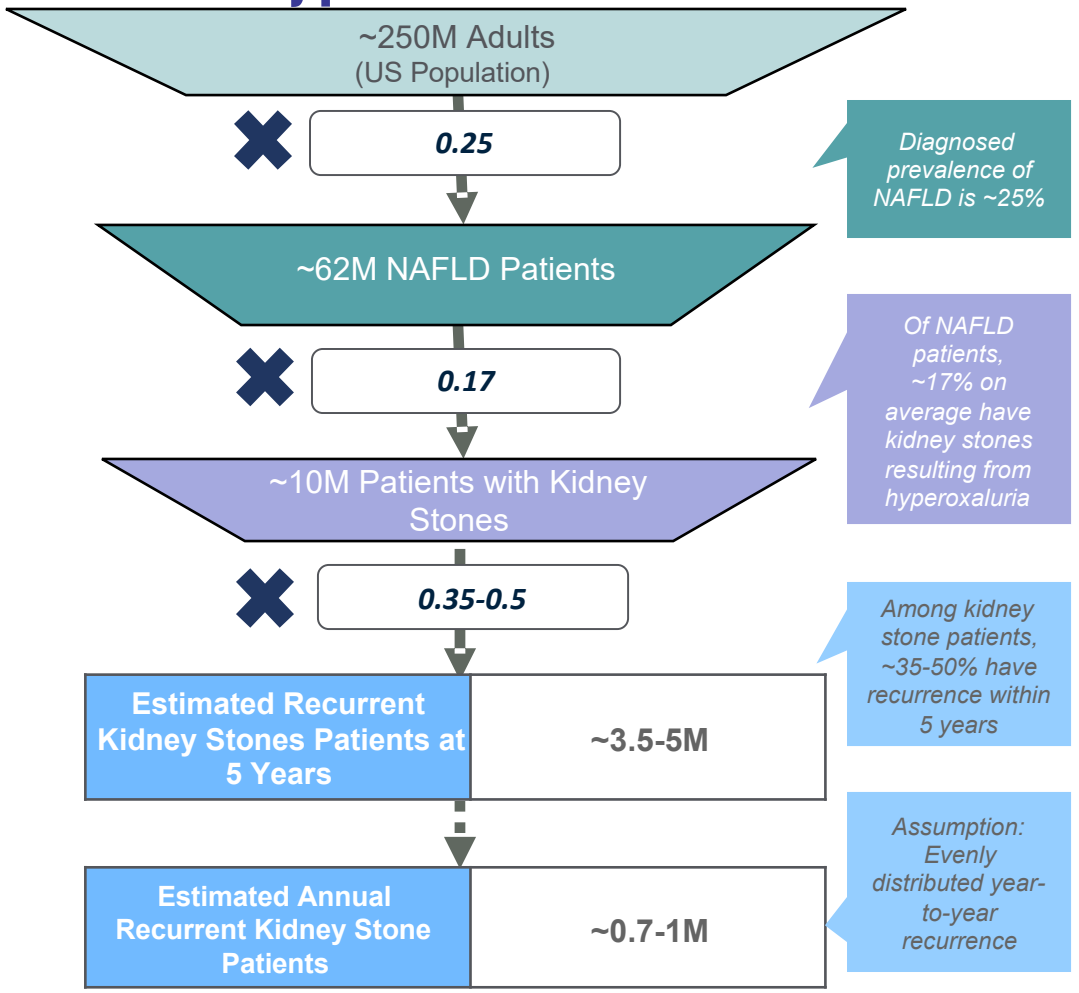
## RECAP & FEEDBACK

# THANK YOU

# US STRATEGIC COUNCIL FOR DEMONSTRATING EFFECTIVENESS

## 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] | • 4,024 individuals aged ≥ 20 years were included in the analysis<br>• NAFLD prevalence was ~12.4% defined by elevated liver enzymes<br>  • *The sensitivity of liver enzyme detection is low since up to ~78% NAFLD patients fall within the normal range* |
| Younossi (2016)[2] | • A global meta-analysis with 8,515,431 adult patients from 22 countries (>94% from US)<br>• NAFLD prevalence in US adults is 24.13%<br>• Global prevalence of NAFLD is 25.24% |
| Nam (2016) [3] | • 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] | • Of 3,719 men enrolled in China, the percentage of NAFLD patients w ith kidney stones w as 8.4% significantly higher than that among patients w ithout NAFLD (6.4%) diagnosed by ultrasonography<br>• The percentage of kidney stones in mild, moderate, and severe NAFLD patients is 14%, 12%, and 6%, respectively |
| Uribarri (1989)[5] | • "Natural cumulative recurrence rate of renal stones" was 14% at 1 year, 35% at 5 years, and 52% at 10 years |
| Ferraro (2017)[6] | • Literature review of 21 RCTs with 2,168 participants in 46 study arms over a median follow-up of 3.2 years<br>• The cumulative risk of recurrence at 5 years was estimated to be about 53%<br>• The median recurrence was 26 per 100 person-years for those undergoing no treatment<br>• 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) |

NAFLD  Kidney Stones due to NAFLD-associated Hyperoxaluria  Recurrent Kidney Stones

Based on BMRN analy sis and assumptions, additional sources in notes

# 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) |
| ***Trial Design Required for P&MA Success*** | | | • **H2H trial** vs. **physicians' choice of treatment**<br>• Demonstrated **H2H superiority** in the **reduction of kidney stones** that **require surgical intervention**<br>• **Trial inclusion criteria** that specify the inclusion of patients with **≥ 2-5 kidney stones per year and ≥ 1 surgical intervention per year**<br>• **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?