## FREELINE

Corporate Presentation August 16, 2021

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Clinical-stage biotechnology company developing transformative AAV-mediated gene therapies for patients suffering from inherited systemic debilitating diseases

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Proprietary capsid enables high protein expression at low doses in humans

Freeline positioned to target diseases perceived as beyond the reach of first-generation AAV gene therapy

Lead product FLT180a for treatment of hemophilia B demonstrated Factor IX activity levels in normal range enabling potential for functional cure<sup>1</sup>

FLT190 for treatment of Fabry disease completed lowest dose cohort; study positioned for dose escalation; plan to share data by year-end

GD

FIX

Fab

FLT201 for treatment of Gaucher disease Type 1 shows promising pre-clinical data; on track to be in clinic by year-end

**X** 

Proprietary protein engineering, analytics and CMC platform that deliver novel, high-quality gene therapy product candidates at commercial scale

 Certain adult hemophilia B patients

In-house research and manufacturing platform enables the delivery of rationally designed novel AAV gene therapy programs



Identify and design novel targets/candidates with high potential to address unmet patient need Proprietary modular manufacturing technology enables rapid development of high quality products De-risked capsid with significant clinical data validating potency, tolerability and durability in humans

# Hemophilia B data validates AAVS3 capsid and platform Our rationally designed AAVS3 capsid enables: Potent liver transduction Very High protein expression Expression Lower dose levels & improved safety margin



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The FLT180a doses listed, 3.8e11, 6.4e11 and 8.32e11 vg/kg are equivalent to 4.5e11, 7.5e11 and 9.75e11 vg/kg respectively under the previous equivalent dosing nomenclature.

1. Pfizer R&D Day Sep 2020 – up to four-year follow-up data in 15 patients from Phase 1/2 trial.

2. Miesback et al; Blood 2018 131:1022-1031.

3. uniQure R&D day June 22, 2021 – 12-month follow-up data in 54 patients from the HOPE-B Phase 3 trial

4. 3.8e11 vg/kg dose: Two patients dosed at this level, with mean value calculated based on following Week 26 FIX activity levels: Patient 1, 44%, Patient 2, 46%.

5. 6.4e11 vg/kg dose: Two patients dosed at this level. Value of Patient 5, 64%. Patient 4 experienced loss of expression due to transaminitis and is not represented on this chart. At Week 26, Patient 4 FIX activity level was 7%, which would result in a mean FIX activity level of 36% for this dose cohort.

6. 8.32e11 vg/kg dose: Four patients dosed at this level, with mean value calculated for three of them based on following Week 26 FIX activity levels: Patient 8, 180%, Patient 9, 190%, Patient 10, 143%. Patient 7, not represented on chart, achieved FIX activity level of 53% at Week 26, which would result in a mean FIX activity level of 142% for this dose cohort. Patient 7 remains in normal range of FIX activity.

7. One patient in the 8.32e11 vg/kg dose cohort, Patient 8, received exogenous FIX for treatment of a traumatic bleed; at the time, this patient's FIX activity level was and remains in the low end of the normal range.

## Robust pipeline in place: On track to have third program in the clinic by end of 2021







### Hemophilia B & A

Verbrinacogene setparvovec (FLT180a): Potential to provide a functional cure by normalizing FIX activity levels

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#### $= \mathbb{R} = \mathbb{R} = \mathbb{R}$ Key learnings from the Phase 1/2 B-AMAZE dose-finding clinical trial



Stable and durable response up to 3 years post-treatment to date



No spontaneous bleeds that required treatment with supplemental FIX<sup>2</sup>





Short course of prophylactic tacrolimus combined with prophylactic prednisone and close monitoring expected to preserve FIX activity levels in the normal range and thereby eliminate the need for FIX supplementation

1. The Company's B-AMAZE trial dose escalated 10 patients across four dose levels. For future data updates, Freeline expects results will be reported using a new dose level nomenclature in the assay for the commercial-scale process in which the former doses of 4.5e11, 7.5e11, 9.75e11, and 1.5e12 vg/kg correspond to 3.8e11, 6.4e11, 8.32e11, and 1.28e12 vg/kg, respectively.

2. One patient in the 6.4e11 vg/kg dose cohort (7.5e11 vg/kg under the previous equivalent dosing nomenclature) lost expression due to transaminitis and resumed FIX prophylaxis.

### FLT180a clinical development plan to accelerated approval

- Six-month Phase 1/2 trial to confirm the dose and immune management regimen for use in a pivotal Phase 3 study
- File accelerated approval using the surrogate endpoint of FIX activity levels combined with demonstration of a positive correlation between 26-week FIX activity levels and 52-week Annualized Bleeding Rate





## Hemophilia A

FLT210 contains the only Factor VIII construct that fits within the carrying capacity of an AAV capsid





#### Key attributes of FLT210

Smallest disclosed liver specific promoter in development



✓

Shortened FVIII gene to reduce expression cassette size

Allows expression cassette to fit within the natural capacity of AAV capsid



Has the potential to deliver **more** stable FVIII activity\*

\*Can only be demonstrated in human trials, which have not yet been conducted.

Note: Hem A candidate nomination reached. Toxicology, CMC and disease animal model confirmation work ongoing.

Sources of construct sizes:

1. As presented at ASGCT (2016) and WFH (2020).

2. As documented in patent (international patent number: WO/2016/025764).

3. McIntosh J, Lenting PJ, Rosales C, et al. Therapeutic levels of FVIII following a single peripheral vein administration of rAAV vector encoding a novel human factor VIII variant. Blood. 2013;121(17):3335-3344.

4. Bunting S, Zhang L, Xie L, et al. Gene Therapy with BMN 270 Results in Therapeutic Levels of FVIII in Mice and Primates and Normalization of Bleeding in Hemophilic Mice. Mol Ther. 2018;26(2):496-509.

AAAA

### Fabry & Gaucher disease

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FLT190 demonstrates increased GLA expression and reduction in pathologic substrate in key tissues in Fabry mouse model





WORLD symposia 2019: Jey Jeyakumar et al. Liver-directed gene therapy corrects Fabry disease in mice.

FLT190 vector genome pseudo-typed with AAV8 in GLA knockout ("GLA KO") mice; Dose: 2e12 vg/kg. Error bars: mean ± SD.

Time point: 16-week disease development prior to treatment; analysis 14 weeks post-treatment. Gb3/Lyso-Gb3 data (n=4, 2 males and 2 females).

1.Untreated wild-type (non-GLA KO) mice.

2. GLA KO mice.

## Phase 1/2 dose-finding trial assessing the safety and efficacy of FLT190 in adult Fabry patients

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Adaptive study design



Low doses of FLT201 in Gaucher mice result in higher expression and increased uptake in tissues affected by Gaucher Type 1 disease

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- Novel GCase variant produced by FLT201 is more stable in plasma than wild-type protein
- This leads to a greater than 20-fold increase in potency vs. wild-type protein and better substrate clearance in key tissues in Gaucher mice

Increased protein stability compared with velaglucerase alpha



Enhanced and sustained GCase uptake observed in key tissues as compared with velaglucerase alpha



Velaglucerase alfa is an Enzyme Replacement Therapy (ERT) for Gaucher disease.

## Gba-deficient mice data demonstrates GCase tissue penetration by FLT201, enzymatic activity & substrate clearance

- Restoration of GCase activity after FLT201 injection was observed in Gba-deficient mice in difficult-to-reach tissues as shown by decreased levels of lyso-GB1 substrate<sup>1</sup>
- Dose-dependent reductions of lyso-GB1 were observed in all tissues analyzed including bone marrow and lung







Data from study conducted in collaboration with Professor Ying Sun (Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA) and presented at the 17<sup>th</sup> Annual WORLDSymposium.

Velaglucerase alpha - an ERT used for Gaucher disease.

AAV8-FLT201 = AAV8 pseudo-typed FLT201 genome.

ERT = Velaglucerase alfa 60 U/kg biweekly (equivalent of the standard of care in humans).

WT = wild-type mice.

Evaluated 12 weeks post-injection.

1. Lack of GCase enzyme in humans leads to the accumulation of lyso-GB1 and Gaucher disease.

\*p≤0.0001

### Milestones

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## Multiple potential near-term value-creating milestones targeted for 2021

### 2021 Objectives

- Hemophilia B Initiate clinical trial sites for the Phase 1/2 dose confirmation trial
- Hemophilia B Present durability data up to 4 years from Phase 1/2 B-AMAZE dose-finding clinical trial
- Fabry Progress dose escalation in Part I of Phase 1/2 dose-finding clinical trial and share data
- Gaucher Initiate Phase 1/2 dose-finding clinical trial
- Hemophilia A Complete IND/CTA-enabling studies

Platform – Further develop plans for Freeline manufacturing facility



## Thank you