REIMAGINING THE TREATMENT OF HEARING LOSS

Investor Event: KOL Perspective on the Potential of Restorative Therapeutics for Sensorineural Hearing Loss

David L. Lucchino
Chief Executive Officer
January 19, 2021
Forward-Looking Statements and Other Disclaimers

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding the treatment potential of FX-322, the Phase 2a clinical trial of FX-322 and the Phase 1b studies in age-related hearing loss and severe SNHL patients, design, pace and timing of enrollment for the Phase 1b studies in age-related hearing loss and severe SNHL, the timing and completeness of data from the Phase 2a clinical trial and Phase 1b studies in age-related hearing loss and severe SNHL, the results and implications of the Phase 1/2 durability of response data, the timing of end of phase 2 meetings with the FDA and future pivotal studies, the ability of our technology platform to provide patient benefit, the impact of COVID-19 on the Company's ongoing and planned clinical trials and business, future milestone and royalty payments under the license and collaboration agreement with Astellas Pharma Inc. ("Astellas"), the sufficiency of the Company's cash, cash equivalents and short-term investments, estimates of the size of the hearing loss population and population at risk for hearing loss, estimates of the commercial opportunity of FX-322 and the impact on existing treatment paradigms, the timing of the demyelination program, and the potential application of the PCA platform to other diseases.

These forward-looking statements are based on management’s current expectations. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: Frequency Therapeutics (the "Company") has incurred and will continue to incur significant losses and is not and may never be profitable; need for additional funding to complete development and commercialization of any product candidate; the Company’s dependence on the development of FX-322; the unproven approach of the PCA platform; the lengthy, expensive and uncertain process of clinical drug development and regulatory approval; limited experience successfully obtaining marketing approval for and commercializing product candidates; the results of earlier clinical trials not being indicative of the results from later clinical trials; differences between preliminary or interim data and final data; adverse events or undesirable side effects; disruptions at the FDA and other regulatory agencies; the impact of the COVID-19 impact; failure to identify additional product candidates; new or changed legislation; failure to maintain Fast Track designation for FX-322 and such designation failing to result in faster development or regulatory review or approval; costly and damaging litigation, including related to product liability, intellectual property or brought by stockholders; dependence on Astellas for the development and commercialization of FX-322 outside of the United States; misconduct by employees or independent contractors; reliance on third parties, including to conduct clinical trials and manufacture product candidates; compliance with laws and regulations, including healthcare and environmental, health, and safety laws and regulations; failure to obtain, maintain and enforce protection of patents and other intellectual property; security breaches or failure to protect personal information; attracting and retaining key personnel; and ability to manage growth.

These and other important factors discussed under the caption "Risk factors" in the Company’s Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 16, 2020 and its other reports filed with the SEC could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management's estimates as of the date of this presentation. While the Company may elect to update such forward-looking statements at some point in the future, it disclaims any obligation to do so, even if subsequent events cause its views to change. These forward-looking statements should not be relied upon as representing the Company’s views as of any date subsequent to the date of this presentation.
I’m noticing and understanding what you’re saying.
Program Panel

Robert Langer, ScD
David H. Koch Institute Professor, Massachusetts Institute of Technology

Lawrence Lustig, M.D.
Chair, Department of Otolaryngology – Head and Neck Surgery, Columbia University

Frank Lin, M.D., Ph.D.
Director, Cochlear Center for Hearing and Public Health, Johns Hopkins Bloomberg School of Public Health

Rene Gifford, Ph.D.
Associate Director of Pediatric Audiology, Director of Cochlear Implant Program, Vanderbilt University

Carl LeBel
Chief Development Officer, Frequency Therapeutics
Today’s Program:
Key Focus Areas

- Importance of addressing speech intelligibility (clarity)
- Impact of hearing loss on overall health and quality of life
- Substantial and growing prevalence of hearing loss
- Near-term, data-rich period for FX-322
The Future of Hearing Loss Treatments

Lawrence R. Lustig MD
Howard W. Smith Professor and Chair
Department of Otolaryngology-Head & Neck Surgery
Columbia University Medical Center
New York Presbyterian Hospital
Conflicts of Interest

None
Outline

Who

How

What
Sensorineural Hearing Loss Types

- Sensory
- Neural
- Strial
- Mixed
Joe Hawkins Presbycusis Formula:

Genetics

Individual hearing = (Ototoxic drugs + noise exposure + age)
Office of the Surgeon General,
Dep’t of the Army, 1957

Figure 13.—Composite curve showing audiometric loss in 100 patients in whom 100 right ears and 99 left ears were tested.
Threshold Shifts

Temporary Vs Permanent
10 Ears
Before and After
2.5 hrs of "Rock-and-Roll" with SPLs reaching 130 db.

Temporary Thresholds Shifts are NOT Temporary!
$\Sigma =$ noise-damaged ear does not `age' at the same rate as the non-noise damaged ear.
Early NIHL exacerbates AHRL when measured by ABR but not DPOAE
Loss of ribbon synapses in noise-exposed (TTS) mice
Cochlear neuropathy in human presbycusis: Confocal analysis of hidden hearing loss in post-mortem tissue

Lucas M. Viana, Jennifer T. O’Malley, Barbara J. Burgess, Dianne D. Jones, Carlos A.C.P. Oliveira, Felipe Santos, Saumil N. Merchant, Leslie D. Liberman, M. Charles Liberman
Hearing Loss Treatments
Hearing Aids
Cochlear Implants
Future Therapies For Hearing Loss
Inner Ear Drug Delivery - HOW

Target(s):
- Hair Cells
- Supporting Cells
- SGNs
- Stria Vascularis
What will we put in the ear?
Inner Ear Therapies going forward…

- Steroids
- Anti-oxidants
- Apoptotic Inhibitors
- “Nanoparticles”
- Small Molecules
- Growth Factors
- Gene Therapy
- Stem Cells
Gene Therapy for Hearing Loss

Vector

Promoter

Gene
Vector Promoter

Modulate signaling pathway (HC regeneration)

Growth factors to drive neuronal growth/survival

Restore absent function
Override defective protein
Inactivate defective Gene (heterozygous)

Genetic Hearing Loss
Hair Cell Regeneration Pathways

- Wnt/β-catenin
- p27^Kip1 inhibition?
- Mitotic regeneration
- Notch inhibition
- Atoh1 overexpression
- Direct transdifferentiation

Atkinson et al Development, 2015
## Hair Cell Regeneration Clinical Trials

<table>
<thead>
<tr>
<th>Novartis</th>
<th>Regain</th>
<th>Pipeline</th>
<th>Frequency Therapeutics</th>
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<tr>
<td>Direct Transdifferentiation</td>
<td>Direct Transdifferentiation</td>
<td>Direct Transdifferentiation</td>
<td>Mitotic Regeneration</td>
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<tr>
<td>CGF166X201</td>
<td>LY3056480</td>
<td>Gamma-secretase Inhibitor</td>
<td>FX-322</td>
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<tr>
<td>Hair Cell regeneration</td>
<td>Hair cell Regeneration</td>
<td>Hair Cell regeneration + synpaptogenesis</td>
<td>Hair Cell regeneration + synpaptogenesis + Wnt/B-catenin pathway</td>
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<tr>
<td>Atoh1 Overexpression</td>
<td>Notch Inhibition</td>
<td>Notch Inhibition</td>
<td>Notch Inhibition</td>
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Challenges going forward…

• Audiometry doesn’t correlate with biology

• Lack of predictive biomarkers

• Many forms of HL (eg genetic) are *rare*
  Need data repositories for patient recruitment
  Universal genetic screening

• PRESERVATION vs REGENERATION
Applications of intracochlear Rx
(from the CI perspective…)

- Preservation of residual hearing during CI surgery (steroids, antioxidants, etc…)

- Improved spiral ganglion survival to improve CI performance

- Regeneration - stem cells, small molecules, gene therapy, etc…

Short Term

Long Term
Hearing Loss in Adults

Epidemiologic Prevalence & Public Health Impact

Frank Lin, MD PhD
Professor, Departments of Otolaryngology, Medicine, Mental Health & Epidemiology
Director, Cochlear Center for Hearing & Public Health
Estimated Number of Individuals with Hearing Loss by Age

American adults are expected to have hearing loss in 2060

- 73.5 Million

Hearing Loss in Adults

Key Public Health Questions

• What are the consequences of HL for older adults?
  - Epidemiology; Health economics

• What is the impact of treating HL?
  - Clinical trials

• How can HL be effectively addressed in society?
  - New policies & approaches to hearing treatment
Hearing Loss & Dementia

Common Cause or Modifiable Risk Factor

Cognitive Load

Hearing Loss

Brain structure/function

Social Isolation

Cognitive Impairment & Dementia

Common pathological process

Grossman et al, Brain Lang, 2002
Armstrong et al, JAMA Oto, 2019
Lin et al, Aging & Mental Health, 2014
Hearing loss in mid & late life identified as the largest potentially modifiable risk factor for dementia
HEALTHCARE UTILIZATION AMONG PERSONS WITH & WITHOUT HEARING LOSS

Over 10 Years, persons with hearing loss had

- 47% Increased Rate of HOSPITALIZATION
- 2.5 Days Longer During HOSPITAL STAYS
- 44% Increased Risk of 30 DAYS READMISSION
- 17% Increased Risk of EMERGENCY DEPARTMENT VISIT

DIFFERENCE IN MEAN TOTAL HEALTHCARE COST AMONG PERSONS WITH & WITHOUT HEARING LOSS

- NO HEARING LOSS
- HEARING LOSS

2 YEARS: $3,852 vs. $14,893
5 YEARS: $11,147 vs. $30,239
10 YEARS: $41,387 vs. $48,198

Total 10 Years: $70,632 vs. $22,434


AARP | Johns Hopkins Bloomberg School of Public Health | Cochlear Center for Hearing and Public Health | OptumLabs
Hearing Loss in Adults

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• How can HL be effectively addressed in society?
  - New policies & approaches to hearing treatment
HL treatment could have potential positive effects on both short-(social function) and longer-term (dementia risk, health care costs) outcomes

- Definitive effects of HL treatment cannot be established through observational studies despite strong suggestive evidence of positive impact of HL treatment

- Ongoing NIH-funded randomized trial (ACHIEVE, n ~1000 adults 70-84 yrs) set to finish in 2023
  - Will provide definitive RCT evidence of impact of HL treatment with hearing aids on risk of cognitive decline/dementia, brain aging, social and physical function, and health care costs

https://clinicaltrials.gov/ct2/show/NCT03243422
Hearing Loss in Adults

Key Public Health Questions

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Scope of untreated hearing loss requires:

• New federal policies around hearing care
  - OTC Hearing Aid Act of 2017 will go into effect in 2021 & lead to new FDA regs for HAs → greater awareness as Bose, etc. enter the HA market
  - Ongoing efforts (e.g., HR 3, HR 4618) to enact Medicare reform would provide hearing care coverage

• New approaches to hearing loss treatment
  - Optimizing conventional rehabilitative options → e.g., alternative care delivery models; innovations in amplification & signal delivery
  - Pharmacological approaches to restore function → paradigm shift
www.jhucochlearcenter.org
flin1@jh.edu
Communication challenges for patients with high-frequency hearing loss

René Gifford, Ph.D., CCC-A

Department of Hearing and Speech Sciences
Department of Otolaryngology—Head & Neck Surgery
Disclosures

• Research and lab funded by NIH NIDCD

• Consultant: Advanced Bionics, Cochlear, Frequency Therapeutics
High Frequency Hearing Loss

Speech sounds
4000-7000+ Hz

/s/  /z/  /v/
/sh/  /ch/  /j/
/t/  /th/  /ee/
/f/  /ng/  /zh/
Diagnostic Audiology
Audiology clinic: #1 complaint

Pure-tone audiogram: detection/sensation

Speech recognition: perception
OTC products

Custom hearing aids

Auditory implants
Cochlear hair cell loss over time

Wu et al. (2019) Neuroscience, 407: 8-20
Summary

Hearing loss: leading cause of overall disability worldwide

466M individuals with disabling hearing loss (WHO, 2018)

Speech perception & detection → more important than audiogram alone

Hearing technology cannot overcome effects of auditory damage
REIMAGINING THE TREATMENT OF HEARING LOSS

Investor Event: KOL Perspective on the Potential of Restorative Therapeutics for Sensorineural Hearing Loss

Dr. Carl LeBel
Chief Development Officer
January 19, 2021
Clinical Development
Focus: FX-322

**Strategic Focus**
Drive toward pivotal studies for restorative SNHL treatment
Build on key learnings from Phase 2a to inform design of potential registrational studies

**Momentum**
Acceptance of clinical data in Otology & Neurotology
**Late Q1 2021**: day-90 read out of FX-322 Phase 2a study
**Late Q2 2021**: end-of-study readout of FX-322 Phase 2a study

**Expansion**
Commenced Phase 1b study in age-related hearing loss (readout Q2 2021)
Commenced Phase 1b study in severe hearing loss patients (readout Q3 2021)
Recap: Completed FX-322 Phase 1/2 Safety Study

**Study Design**

- Single Injection: 15 drug, 8 placebo
- No Injection: All 23 patients

Injection only in one ear creating an additional control

- Safety study
- Patients with mild to moderate SNHL; permanent NIHL/SSNHL for at least 6 months
- Majority of patients did not have measurable impairment in WR

**Key Findings**

- FX-322 shown to have a favorable safety profile – no serious AEs
- Clinically meaningful improvement in word recognition scores in patients with measurable word recognition deficits
- Statistically significant improvement in word recognition scores (words in quiet/sound clarity)
- Improvement trend in words-in-noise

**Graphs**

- Absolute Word Recognition Scores
- % Change from Baseline in Word Recognition Scores
- % Change from Baseline in Words-in-Noise Scores
FX-322 Patients Show Sustained Hearing Improvements 13-21 Months After Initial Dosing

Key Findings

• Preliminary evidence indicating a durable benefit of hearing clarity

Baseline - Correct words out of 50
Day 90 - Correct words out of 50
1-2 Years - Correct words out of 50

Three patients who had durable improvements in intelligibility also had pure tone audiometry improvements of 10 – 15 dB at the highest frequency tested (8k Hz)

- *25W = 25 Word test performed outside an official study site at 13-18 months after dosing; results scaled to 50 words
- 50W = 50 Word test performed under a formal protocol at original study site at 18-21 months after dosing
- **Since FX-322 dosing
**FX-322 Study - Phase 2a Design**

- **Screening NIHL/SSNHL Mild to Moderately Severe**
- **Randomize 1:1:1:1**
  - FX-322 1X N = 24
  - FX-322 2X N = 24
  - FX-322 4X N = 24
  - Placebo 4X N = 24
- **Weekly Dosing**
- **Follow-up Visits**
  - Days 15, 30, 60, 90, 120, 150, 180, 210

- All patients have stable hearing loss
- Patient etiologies/age similar to Phase 1/2 study
- All patients have word recognition impairment
- >95% completed all study visits
### Collecting Key Data to Inform Clinical Program

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<thead>
<tr>
<th>Phase 1/2 Study</th>
<th>Phase 2a Study Overview</th>
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<tbody>
<tr>
<td><strong>N= 23</strong></td>
<td><strong>N= 95</strong></td>
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<tr>
<td><strong>Safety Study: Hearing restoration signal observed</strong></td>
<td><strong>Confirm signal and validate potential endpoints</strong></td>
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<tr>
<td>Word recognition/Words-in-noise</td>
<td>Word recognition/Words-in-noise</td>
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<tr>
<td>Pure tone audiometry at 8kHz (0.25-8kHz)</td>
<td>Pure tone audiometry (0.25-16kHz)</td>
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<tr>
<td><strong>Entrance criteria limited subjects</strong> with meaningful word recognition/words-in-noise deficits</td>
<td><strong>Entrance criteria requires all subjects</strong> have meaningful word recognition deficits</td>
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<td>Single dose</td>
<td>Single and multiple doses</td>
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Studies are double-blind, placebo-controlled, multi-center, in adults ages 18-65
Phase 2a Readouts: Data to be Provided at Day-90 and End of Study

**FX-322 day-90 group-level data review (late Q1 2021)***:

- Speech **intelligibility** as measured by WR and WIN testing
- Pure Tone Audiometry measures at **frequencies from 0.25Hz to 16k Hz**
- Partial data on measures of FX-322 on **tinnitus, impact on QoL**
- **Safety** profile

**FX-322 end-of-study group- and individual-level data readout (late Q2 2021)**:

- **Full (7 month)** intelligibility and audibility data.
- Seven-month **durability data** (all patients)
- Full study data on measures of FX-322 on **tinnitus, impact on QoL**
- **Safety** profile

*Data analysis to include but not be limited to:

- Absolute difference between groups
- Relative percent change from baseline
- Absolute percent change from baseline
- Responder analysis (proportion of patients with a change)
- Categorical analysis based on severity
Phase 2a Study objectives

- Further establish hearing signal
- Evaluate repeat dosing
- Clarify endpoints and patient population for registration

Improvements in key intelligibility measures such as word recognition and words in noise

FX-322 impact on secondary measures including ultra-high frequency pure tones, tinnitus and QOL measures
Program to Address Broadest Patient Population

Each SNHL Type Being Studied in FX-322 clinical program represents a significant patient population.

Prevalent Hearing Loss Population (~41 MM)
~10% growth by 2030

- 5M severe
- 16M mild to moderate, age 65+
- 20M mild to moderate, age 18-65

Phase 1b Study evaluating ages 18-65 with severe hearing loss

Phase 1b Study evaluating ages 66-85 with mild to moderately severe age-related hearing loss

Phase 2a Study evaluating ages 18 – 65 with noise induced and sudden mild to moderately severe SNHL

Source: NCHS Survey Data 2016-18, NCHS 2017; NCHS 2016;
## FX-322 Timeline for 2021:
Multiple Data Readouts Anticipated to Inform Late-Stage Development

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<td>Day-90 FX-322 P2a data</td>
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<td>P1b age-related study readout</td>
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<td>End of Phase 2a study readout</td>
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<td>P1b severe hearing loss study readout</td>
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- FDA EOP2 Meeting
- Design of late-stage clinical development plan