Voretigene Neparvovec (Voretigene) for Confirmed Biallelic RPE65 Mutation-Associated Retinal Dystrophy

October 12, 2017
Spark Therapeutics
Cellular, Tissue and Gene Therapies Advisory Committee
Introduction

Katherine High, MD
President and Head of Research and Development
Spark Therapeutics
## Agenda

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<td>Katherine High, MD</td>
<td>President and Head of Research and Development Spark Therapeutics</td>
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<td>Unmet Need</td>
<td>Mark Pennesi, MD, PhD</td>
<td>Associate Professor in Ophthalmic Genetics Oregon Health and Science University (OHSU)</td>
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<td>Kathleen Reape, MD</td>
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<td>Deborah Kelly, MD</td>
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<td>Albert Maguire, MD</td>
<td>Clinical Associate in Division of Pediatric Ophthalmology Children's Hospital of Philadelphia (CHOP)</td>
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# Additional Experts

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<th>Category</th>
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<th>Institution</th>
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<tr>
<td>Pre-clinical and clinical development programs</td>
<td>Jean Bennett, MD, PhD</td>
<td>University of Pennsylvania</td>
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<td>Community-based functional vision assessment</td>
<td>Duane Geruschat, PhD</td>
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<tr>
<td>Neuroscientist</td>
<td>Chris Johnson, PhD</td>
<td>University of Iowa</td>
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<tr>
<td>Principal investigator</td>
<td>Steve Russell, MD</td>
<td>University of Iowa</td>
</tr>
<tr>
<td>Genetic counseling</td>
<td>Karmen Trzupek, MS, CGC</td>
<td>InformedDNA</td>
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<td>Trial investigator</td>
<td>Julia Haller, MD</td>
<td>Wills Eye Hospital</td>
</tr>
<tr>
<td>Statistics</td>
<td>Fan-Fan Yu, ScD</td>
<td>Statistics Collaborative, Inc</td>
</tr>
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</table>
Voretigene Neparvovec Subretinal Injection

- Improves functional vision and visual function in patients with biallelic RPE65 mutation-associated retinal dystrophy
- Progressive disease eventually leads to complete blindness in nearly all patients
- No treatment options
Voretigene Supplies Functional RPE65 Enzyme Resulting in Restoration of Visual Cycle

[Diagram showing the visual cycle and the target location of RPE65 expression in photoreceptor cells.]
Voretigene Product: Adeno-Associated Viral Type 2 (AAV2) Gene Therapy Vector

- AAV2 efficiently transduces RPE cells
- AAV clinical experience for over two decades
- Drives expression of cDNA encoding human retinal pigment epithelium 65 kDa (RPE65) protein

vg/mL: vector genomes per milliliter
Voretigene Manufacturing Results in Full Vector Particles

- Triple transfection of HEK293 cells
- Downstream purification process separates empty AAV capsids from full AAV capsids
  - Essentially only full particles administered in final product
- Formulated in physiologic buffer containing surfactant to prevent loss of vector on product contact surfaces
Voretigene Dosing and Administration

- Sequential, bilateral, subretinal injection
  - 1.5E11 vg in 0.3 mL total subretinal volume per eye
- Eyes administered 6 to 18 days apart
  - Identify potential early-emergent surgical complications prior to second eye administration
  - Reduces risk of immune response
- Injection location identified via imaging
## Regulatory History Related to Evolving Understanding of RPE65 Mutation-Associated Retinal Dystrophy

<table>
<thead>
<tr>
<th>Year</th>
<th>Action</th>
</tr>
</thead>
</table>
| 2008 | Orphan drug designation  
• Treatment of LCA due to *RPE65* mutations |
| 2011 | Advisory Committee on cell and gene therapies for retinal disorders recommended novel endpoints for functional vision |
| 2014 | Breakthrough designation |
| 2016 | Orphan drug designation amendment  
• Treatment of IRD due to biallelic *RPE65* mutations |
Voretigene Clinical Development Program

- **RPE65 Mutation-Associated Retinal Dystrophy Subjects**
  - Study 101 / 102 (Phase 1)
    - N=12
  - Study 301 (Phase 3)
    - N=31
  - Natural History Study

- **IRD and Normal-Sighted Subjects**
  - Multi-Luminance Mobility Test (MLMT) Validation Study

- All Phase 1 and Phase 3 subjects enrolled in 15 year follow-up study
Voretigene Clinical Results

- Clinically meaningful and statistically significant improvements in functional vision, light sensitivity, and visual function
  - Improvement observed as early as 30 days
  - Response maintained for up to 3 years
  - Repeat administration
    - Not warranted based on durability of Phase 3 data
    - Not studied in clinical development; theoretical risks
- Safety profile consistent with this type of procedure
  - Safety followed for up to 9 years
Proposed Voretigene Indication

- For treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy
  - With sufficient viable retinal cells, which can be estimated by optical coherence tomography (OCT) as an area of retina within the posterior pole of > 100 micron thickness

- Patients ≥ 3 years old
Unmet Need in Biallelic RPE65 Mutation-Associated Retinal Dystrophy

Mark Pennesi, MD, PhD
Associate Professor, Ophthalmic Genetics
Oregon Health and Science University
Presentation Overview

- Disease background
- Evaluation of vision
- Impact
Inherited Retinal Degenerations (IRD) Caused by > 250 Different Genes

- Congenital Stationary Night Blindness
- Retinitis Pigmentosa
- Usher Syndrome
- Leber Congenital Amaurosis
- Cone/Cone-Rod Dystrophies
- Bardet-Biedel Syndrome
RPE65 Mutation-Associated Retinal Dystrophy
~7-9% of LCA and ~1-2% of RP Cases
Biallelic Mutations in *RPE65* Prevent Regeneration of Rod Visual Pigment

- Rod photoreceptor dysfunction
  - Nyctalopia or night blindness
  - Inability to see or perceive in dim light
- Cone photoreceptors secondarily affected
  - Color vision loss
- Eventually nearly all patients progress to complete blindness
Prevalence of *RPE65* Mutation-Associated Retinal Dystrophy

- ~1,000-2,000 patients affected in US\(^1\)
- Many patients visually compromised in early childhood
  - Some diagnosed later when parents notice symptoms

RPE65 Mutation-Associated Retinal Dystrophy
Often Labeled with Variety of Terms

- LCA 47.4%
- RP 7.7%
- SECORD 5.1%
- Tapetal Retinal Dystrophy 6.4%
- Low Vision 3.8%
- EOSRD 2.6%
- Tapetal Retinal Dystrophy, Leber Type 3.8%
- RPE65-related LCA 2.6%
- Cone Rod Dystrophy 2.6%
- Other 20.5%
Presentation Overview

- Disease background
- Evaluation of vision
- Impact
Visual Function vs. Functional Vision

Visual Function

Visual Acuity

Visual Fields

Contrast, Light/Dark Adaptation

Integration

Functional Vision

Reading

Mobility / Navigation
Presentation Overview

- Disease background
- Evaluation of vision
- Impact
Natural History Study of *RPE65* Mutation-Associated Retinal Dystrophy

- Rare disease with limited natural history data
- Retrospective chart reviews of 70 patients with confirmed *RPE65* mutations
Natural History Study Suggests Early, Profound Visual Acuity Changes

Holladay 2004 (right eye)

p < 0.001

Worsening

LogMAR

Age Range (years)


20/20

20/200 - Legal blindness

20/20,000

p < 0.001
Example of Patient’s Visual Field Progression

<table>
<thead>
<tr>
<th>Age 6</th>
<th>Age 12</th>
<th>Age 18</th>
<th>Age 23</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Right Eye Age 6" /></td>
<td><img src="image2" alt="Right Eye Age 12" /></td>
<td><img src="image3" alt="Right Eye Age 18" /></td>
<td><img src="image4" alt="Right Eye Age 23" /></td>
</tr>
<tr>
<td><img src="image5" alt="Left Eye Age 6" /></td>
<td><img src="image6" alt="Left Eye Age 12" /></td>
<td><img src="image7" alt="Left Eye Age 18" /></td>
<td><img src="image8" alt="Left Eye Age 23" /></td>
</tr>
</tbody>
</table>
RPE65-Mediated IRD Vision Loss Progression – Daytime

VISUAL ACUITY LOSS
DECREASED COLOR CONTRAST

Images presented for illustrative purposes only
CO-30

RPE65-Mediated IRD Vision Loss Progression – Daytime

VISUAL FIELD LOSS

Images presented for illustrative purposes only
DECREASED LIGHT SENSITIVITY
CO-33

RPE65-Mediated IRD Vision Loss Progression – Nighttime

VISUAL FIELD LOSS

Images presented for illustrative purposes only
Impact of Disease on Functional Vision
Patients with *RPE65* Mutation-Associated Retinal Dystrophy Suffer from Severe and Progressive Disease

- > 50% legally blind by age 16
- 100% legally blind by age 34
- Most progress to complete blindness
- No available treatments
Need for Effective Treatment for Patients with 
*RPE65* Mutation-Associated Retinal Dystrophy

- Results from loss of RPE65 protein
- Gene therapy holds promise for restoring functional RPE65 protein and increasing retinal sensitivity
  - Better functional vision
- Treatment can improve ability to navigate safely and gain independence
- Without treatment patients will go legally or completely blind
Efficacy

Kathleen Reape, MD
Head of Clinical Research and Development
Spark Therapeutics
Voretigene Efficacy Overview

- Voretigene resulted in clinically meaningful and highly statistically significant improvements compared to control
  - Functional vision
  - Light sensitivity
  - Visual function
- Early improvements observed by Day 30
- Durability of response demonstrated up to 3 years
Multi-Luminance Mobility Test (MLMT)
MLMT: Developed to Measure Functional Vision

- Developed after discussions with the FDA
  - Navigate course independently and accurately within time limit
  - Integrates input from visual acuity (VA), visual field (VF) and light sensitivity
- Designed for use in pediatric and adult populations
- Conducted at 7 different light levels ranging from 1-400 lux
MLMT: Designed to Detect Changes in Functional Vision in Dim Light

<table>
<thead>
<tr>
<th>Light Levels</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 lux</td>
<td>Indoor nightlight; Moonless summer night</td>
</tr>
<tr>
<td>4 lux</td>
<td>Cloudless night with half moon; Parking lot at night</td>
</tr>
<tr>
<td>10 lux</td>
<td>1 hour after sunset in city; Bus stop at night</td>
</tr>
<tr>
<td>50 lux</td>
<td>Outdoor train station at night; Inside of lighted stairwell</td>
</tr>
<tr>
<td>125 lux</td>
<td>30 minutes before sunrise; Interior of train / bus at night</td>
</tr>
<tr>
<td>250 lux</td>
<td>Interior of elevator or office hallway</td>
</tr>
<tr>
<td>400 lux</td>
<td>Office environment or food court</td>
</tr>
</tbody>
</table>

Images presented for illustrative purposes only
Light meter: National Institute of Standards and Technology-calibrated, Extech model #EA33 light meters used to provide examples and to set / verify specified light levels used for mobility testing
MLMT: 12 Different Course Layouts
MLMT: Testing Procedures

- Need to complete course within fixed time, with few errors
  - Lowest possible light level
  - Right eye, left eye, and both eyes tested
- All tests videotaped, coded and randomly evaluated by masked graders
  - Scoring by 2 independent, central graders
MLMT: Result Determined by Accuracy and Time

- Accuracy: 3 errors maximum
  - Obstacles hit, course deviations, arrows bypassed
- Maximum time: 3 minutes (including time penalties)

<table>
<thead>
<tr>
<th>Accuracy (Errors)</th>
<th>Time (with penalties)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>Fail</td>
<td>Fail</td>
</tr>
<tr>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>Fail</td>
<td>Fail</td>
</tr>
<tr>
<td>Fail</td>
<td>Fail</td>
</tr>
</tbody>
</table>
## MLMT: Score Change from Baseline to Year 1

*Used to Quantify Performance*

<table>
<thead>
<tr>
<th>Light Levels</th>
<th>Score</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 lux</td>
<td>6</td>
<td>PASS</td>
</tr>
<tr>
<td>4 lux</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>10 lux</td>
<td>4</td>
<td>FAIL</td>
</tr>
<tr>
<td>50 lux</td>
<td>3</td>
<td>PASS</td>
</tr>
<tr>
<td>125 lux</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>250 lux</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>400 lux</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**YEAR 1 SCORE = 6**

**MLMT SCORE CHANGE = 3**

**BASELINE SCORE = 3**
MLMT: Validation Study

- Designed to characterize construct and content validity
- 26 normal-sighted, 28 inherited retinal dystrophy (IRD)
- Normal-sighted participants
  - Baseline results consistent at 1 year
  - 26 (100%) passed at lowest level (1 lux)
- IRD patients
  - No improvements observed from baseline to 1 year
  - 8 (28.5%) patients declined in performance over 1 year
MLMT Validation Study: Performance Relates to Visual Acuity (VA) and Goldmann Visual Fields (GVF)

- **Visual Acuity**
  - VA 20/63 (0.5 logMAR) or better: more likely to pass
  - VA 20/2000 (2.0 logMAR) or worse: more likely to fail

- **Goldmann Visual Fields**
  - Measured in sum total degrees (1200-1400 normal)
  - For GVF less than 500 sum total degrees: more likely to fail
Mobility Test Study Results Support Use of MLMT to Measure Functional Vision in Patients with IRDs

- Differentiate low vision from normal-sighted controls
- Detect changes in performance over time
- Identify wide range of performance among visually impaired
- High reproducibility
  - > 4000 videos evaluated
- Demonstrated construct and content validity
Phase 3 Trial
Phase 3: Multi-Center, Open-Label, Randomized, Controlled Study

Dose: 1.5E11 vg (volume 0.3 mL) per eye
Timing: 6 to 18 days between injections

Randomization (2:1)

Intervention (N=21 ITT)

1<sup>st</sup> Eye Injected

2<sup>nd</sup> Eye Injected

Follow-up Visits

Crossover to Intervention (Control/Intervention)

Control (N=10 ITT)

Endpoint Reached Year 1

mITT (N=29): 1 Control patient withdrew consent; personal reasons. 1 Intervention patient withdrawn by physician; severe retinal atrophy.
Phase 3: Enrollment Criteria

- ≥ 3 years old with confirmed RPE65 mutations
- Visual acuity ≤ 20/60 or visual field < 20° in any of 24 meridians for each eye
- Sufficient viable retinal cells by noninvasive means
- Ability to comprehend MLMT, follow course instructions and capacity to successfully navigate
- Unable to pass MLMT at lowest light level
Phase 3: Primary and Secondary Endpoints

- Primary endpoint
  - Bilateral MLMT score change at Year 1
- Secondary endpoints (hierarchically tested)
  - Full-field light sensitivity threshold (FST) testing
  - MLMT score change (monocular)
  - Visual acuity
Phase 3: Statistical Analysis Plan

- Minimum sample size = 24 (16 Intervention, 8 Control)
  - 90% power to detect 1 light level change in MLMT
- Primary analysis used a non-parametric permutation test based on a Wilcoxon rank-sum test statistic
  - Two-sided Type I error rate of 0.05
Phase 3: Trial Disposition

Randomization (N=31)

Intent-to-Treat ITT

Modified Intent-to-Treat mITT / Safety

Control (N=10)

N=1 Patient withdrawal: Personal reasons

Intervention (N=21)

N=1 Physician withdrawal: Severe retinal thinning

N=20

N=9
<table>
<thead>
<tr>
<th>Category</th>
<th>Intervention (N=21)</th>
<th>Control (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age at Randomization (Range)</td>
<td>14.7 (4 – 44)</td>
<td>15.9 (4 – 31)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (43%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>14 (67%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (14%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>2 (10%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Ethnicity (Not Hispanic)</td>
<td>16 (76%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>US Resident</td>
<td>17 (81%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Baseline Bilateral MLMT (median)</td>
<td>50 lux</td>
<td>50 lux</td>
</tr>
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</table>
## Phase 3: Efficacy Endpoints (ITT) Results

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Measurement</th>
<th>Difference (95% CI) (Intervention-Control)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLMT performance</td>
<td>Bilateral, score change (difference in means)</td>
<td>1.6 (0.72, 2.41)</td>
<td>p = 0.001</td>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FST testing, white light</td>
<td>Averaged over both eyes, log10 (cd.s/m²)</td>
<td>-2.11 (-3.19, -1.04)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>MLMT performance</td>
<td>Assigned first eye, score change (difference in means)</td>
<td>1.7 (0.89, 2.52)</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>Averaged over both eyes, LogMAR (Holladay)</td>
<td>-0.16 (-0.41, 0.08)</td>
<td>p = 0.17</td>
</tr>
<tr>
<td><strong>Additional Exploratory Endpoint</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Visual field</td>
<td>Goldmann III4e sum total degrees, averaged over both eyes</td>
<td>378.7 (145.5, 612.0)</td>
<td>Nominal p = 0.006</td>
</tr>
</tbody>
</table>
Phase 3: MLMT Results Maintained Through Year 2

Improvement

MLMT Lux Score
Bilateral Testing

(1 lux) 6
(4 lux) 5
(10 lux) 4
(50 lux) 3
(125 lux) 2

Control/Intervention (N=9)
Original Intervention (N=20)
Control (N=9)

* p = 0.004; mITT
Intervals are +/- 1 standard error
Prespecified Primary Endpoint
Phase 3: Overall Durability of Response Observed Throughout Long-Term Follow-Up

![Graph showing improvement over time in Lux Score with data points for Original Intervention (N=5).](image-url)

May 18, 2016 data cutoff
Intervals are +/- 1 standard error
## Phase 3: MLMT Time to Completion, Averaged Over Lux Levels, (mITT) Intervention vs. Control

<table>
<thead>
<tr>
<th>Bilateral Time to Complete (sec)</th>
<th>Intervention (N=20)</th>
<th>Control (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Year 1</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>101.1 (41.7)</td>
<td>49.0 (35.6)</td>
</tr>
</tbody>
</table>
Phase 3: MLMT Baseline and Year 1 Performance

Bilateral Mobility Testing: Injection Baseline at 1 lux

Time to Completion: 214 seconds

Bilateral Mobility Testing: Year 1 at 1 lux

Time to Completion: 17 seconds
Phase 3: MLMT Individual Results at Year 1 by Treatment Group

Original Intervention:
- 19 of 20 (95%) improved by ≥ 1 light level
- 11 of 20 (55%) improved by ≥ 2 light levels
- 13 of 20 (65%) achieved the maximum lux score

Control – After Treatment:
- 8 of 9 (89%) improved by ≥ 1 light level and achieved the maximum lux score
- 5 of 9 (56%) improved by ≥ 2 light levels
Phase 3: 27 of 29 Patients Experienced Significant Improvement in Functional Vision at Lower Light Levels

27 of 29 (93%) improved by ≥ 1 light level
16 of 29 (55%) improved by ≥ 2 light levels
21 of 29 (72%) achieved the maximum lux score
Phase 3: Secondary Endpoint FST
> 100-Fold Improvement in White Light Sensitivity

* p < 0.001; mITT
Intervals are +/- 1 standard error

Prespecified Secondary Endpoint
Phase 3: Secondary Endpoint MLMT 1st Eye

- Improvement
- MLMT Lux Score 1st Eye Testing

- (1 lux) 6
- (4 lux) 5
- (10 lux) 4
- (50 lux) 3
- (125 lux) 2

Study Visit:
- BL
- D30
- D90
- D180
- Y1*
- Y2
- Y1

- Control/Intervention (N=9)
- Original Intervention (N=20)
- Control (N=9)

* p = 0.001; mITT
Intervals are +/- 1 standard error

Prespecified Secondary Endpoint
Phase 3: Secondary Endpoint VA (Holladay) – Averaged Across Both Eyes

Study Visit

- **Control/Intervention (N=9)**
- **Original Intervention (N=20)**
- **Control (N=9)**

* p = 0.27; mTT
Intervals are +/- 1 standard error

Prespecified Secondary Endpoint
Phase 3: Visual Field Testing Supports Clinical Relevance of Voretigene Therapy (Goldmann)

Goldmann VF III4e (Sum Total Degrees)

- Control/Intervention (N=9)
- Original Intervention (N=20)
- Control (N=9)

Study Visit

BL D30 D90 D180 Y1* BL D30 D90 D180 Y2

* p = 0.006; mITT
Intervals are +/- 1 standard error
Visual Function Questionnaire
Visual Function Questionnaire (VFQ)

- Based on National Eye Institute VFQ-25
  - Modified for pediatric population and those with extremely poor vision
- 25 questions pertaining to activities of daily living
  - 10 point scale for each question (0 being most difficult)
- Average of all responses determines score for each participant
## Visual Function Questionnaire Results for Patients (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=21)</th>
<th>Control (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Average Score</td>
<td>4.4</td>
<td>4.9</td>
</tr>
<tr>
<td>Year 1 Average Score</td>
<td>7.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>2.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Nominal p-value</td>
<td>p = 0.001</td>
<td></td>
</tr>
</tbody>
</table>
Overall Benefit of Voretigene for Patients with RPE65 Mutation-Associated Retinal Dystrophy

- Primary endpoint met supporting significant improvement in functional vision at lower light levels
- Secondary and additional endpoints support benefit across range of visual function tests
- Control/Intervention patients support robustness of results
- Durability of response up to 3 years follow-up
Safety

Deborah Kelly, MD
Head of Pharmacovigilance
Spark Therapeutics
Voretigene Safety Overview

- Safety profile consistent with vitrectomy and subretinal injection procedure
- Followed for up to 9 years
- Risk management plan designed to
  - Support appropriate administration
  - Collect long-term safety data
Clinical Development Included 41 Patients Who Received Voretigene in 81 Injected Eyes

<table>
<thead>
<tr>
<th>Study</th>
<th>Voretigene Dose Cohorts (Number of Eyes Exposed)</th>
<th>Total Eyes Exposed</th>
<th>Total Patients Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5E10 vg</td>
<td>4.8E10 vg</td>
<td>1.5E11 vg</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>6</td>
<td>72</td>
</tr>
<tr>
<td>Phase 1</td>
<td>3</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>101 (1st Eye)</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>102 (2nd Eye)</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>Phase 3</td>
<td>-</td>
<td>-</td>
<td>58</td>
</tr>
</tbody>
</table>

* One patient did not meet eligibility criteria for administration in the contralateral eye
All Patients from Clinical Development Program Enrolled in 15-Year Follow-Up Study

<table>
<thead>
<tr>
<th>Last Study Visit Completed</th>
<th>Phase 1 Patients (N=12)</th>
<th>Phase 3 Patients (N=29)</th>
<th>Total (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>12</td>
<td>29</td>
<td>41</td>
</tr>
<tr>
<td>Year 2</td>
<td>12</td>
<td>29</td>
<td>41</td>
</tr>
<tr>
<td>Year 3</td>
<td>12</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>Year 4</td>
<td>12</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Year 5</td>
<td>12</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Year 6</td>
<td>12</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Year 7</td>
<td>12</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Year 8</td>
<td>8</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Year 9</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

Three patients, two from Phase 1 and one from Phase 3 are now completing annual visits by phone call
### Overview of Adverse Events

**Data cutoff May 5, 2017**

<table>
<thead>
<tr>
<th></th>
<th>Voretigene Treated Patients</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase 1</td>
<td>Phase 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7-9 years follow-up (N=12)</td>
<td>2-4 years follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(N=29)</td>
<td></td>
</tr>
<tr>
<td><strong>Any AE</strong></td>
<td>12</td>
<td>29</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Any AE of Maximum Severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>4</td>
<td>10</td>
<td>34%</td>
</tr>
<tr>
<td>Moderate</td>
<td>6</td>
<td>15</td>
<td>52%</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>4</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Any SAEs</strong></td>
<td>5</td>
<td>4</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Any Ocular AEs</strong></td>
<td>11</td>
<td>19</td>
<td>66%</td>
</tr>
</tbody>
</table>
Phase 1 SAEs Reported Over 7-9 Years

- Anal fistula
- Cryptorchism
- Paraesthesia
- Lower limb fracture
- Increased IOP
Phase 1 SAE: Increased IOP

- 1 event 151 days post-administration
  - Related to periocular steroid
  - Endophthalmitis
    - Treated with anti-infectives and periocular steroid injection with prompt resolution
  - 3 months post-administration IOP > 30mmHg
    - Subsequently AE of optic atrophy reported
Phase 3 SAEs Reported Over 2-4 Years

- Convulsion (pre-existing condition)
- Adverse drug reaction to anti-seizure medication
- Adverse drug reaction to anesthesia from oral surgery
- Menorrhagia
- Pneumonia
- Retinal disorder
Phase 3 SAE: Retinal Disorder

- 1 event
  - Related to administration procedure
  - Loss of foveal function 34 days post-administration
  - Thinning of central retina with VA loss, unresolved by 1 year
Ocular Adverse Events of Special Interest

- Macular disorders
- Intraocular pressure increased
- Retinal tear
- Intraocular infections / inflammation
- Cataract
# Ocular AESI: Macular Disorders

<table>
<thead>
<tr>
<th>Preferred Term (verbatim)</th>
<th>Eyes (N=81)</th>
<th>Patients (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular Disorders</td>
<td>9 (11%)</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>Macular Hole</td>
<td>3 (4%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Macular Degeneration (Macular Thinning)</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Eye Disorder (Foveal Dehiscence)</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Maculopathy (Epiretinal Membrane, Macular Pucker)</td>
<td>3 (4%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Retinal Disorder (Foveal Thinning, Loss of Foveal Function)</td>
<td>2 (2%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

- 4 events unresolved (1 macular hole, 3 maculopathy)
- Related to administration procedure
## Ocular AESI: Intraocular Pressure Increased

<table>
<thead>
<tr>
<th></th>
<th>Eyes (N=81)</th>
<th>Patients (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular Pressure Increased</td>
<td>10 (12%)</td>
<td>8 (20%)</td>
</tr>
</tbody>
</table>

- Related AEs mild or moderate in severity
- Most transient and resolved without sequelae
- Most events related to administration procedure

Data cutoff May 5, 2017
Ocular AESI: Retinal Tear

- Observed and repaired by surgeon with laser during procedures
  - One Phase 1 patient, three Phase 3 patients
- All events non-serious and resolved without sequelae
- Related to administration procedure

<table>
<thead>
<tr>
<th></th>
<th>Eyes (N=81)</th>
<th>Patients (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal Tear</td>
<td>4 (5%)</td>
<td>4 (10%)</td>
</tr>
</tbody>
</table>

Data cutoff May 5, 2017
Ocular AESI: Intraocular Infections / Inflammation Related to the Procedure

<table>
<thead>
<tr>
<th>Intraocular Infections / Inflammation</th>
<th>Eyes (N=81)</th>
<th>Patients (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (6%)</td>
<td>3 (7%)</td>
</tr>
</tbody>
</table>

- One event of culture-positive endophthalmitis
- All events considered non-serious
- All events related to administration procedure
- All events resolved

Data cutoff May 5, 2017
## Ocular AESI: Cataract

<table>
<thead>
<tr>
<th>Event</th>
<th>Eyes (N=81)</th>
<th>Patients (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>16 (20%)</td>
<td>9 (22%)</td>
</tr>
</tbody>
</table>

- All events non-serious
  - Elective cataract extraction performed for 7 of 16 events
  - 9 eyes in 5 patients ongoing
- Most considered related to administration procedure
Topic of Interest: Retinal Thinning Occurred Early but Resolved 1 Year Post-Administration

Heidelberg Foveal Thickness (Microns) Change from Baseline for Both Eyes

Phase 3 Study (N=29)
Baseline Mean Foveal Thickness = 185.2 Microns
Intervals are +/- 1 standard error
Voretigene Safety Profile Consistent with Administration Procedure

- Most ocular AEs occurred early and resolved over time
  - Minimal to no intervention
  - Known complications of intraocular surgery
- 2 ocular SAEs; led to loss of visual acuity
  - 1 related to administration procedure
  - 1 known adverse reaction to concomitant medication
Risk Management Plan
Activities to Enhance Surgical Expertise and Clinical Experience

- Supplied to 5 to 8 Centers of Excellence with expertise in IRDs
  - Only healthcare professionals who complete training program
- Surgical training program and manual
  - In-person workshop with principal investigators
- Pharmacy training program and manual
Activities to Monitor Long-Term Safety of Voretigene and Administration: Ongoing Follow-up Study

- All clinical trial patients enrolled in 15-year follow-up study

<table>
<thead>
<tr>
<th>Safety Assessments</th>
<th>Efficacy Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual history</td>
<td>MLMT</td>
</tr>
<tr>
<td>Physical exam</td>
<td>FST</td>
</tr>
<tr>
<td>Ophthalmic exam</td>
<td>Visual acuity</td>
</tr>
<tr>
<td>Clinical labs</td>
<td>Visual function questionnaire</td>
</tr>
<tr>
<td></td>
<td>Visual field</td>
</tr>
</tbody>
</table>
Activities to Monitor Long-Term Safety of Voretigene and Administration: Post-Approval Registry

- Prospective, observational safety registry
  - All patients treated in the first 5 years
  - 5 years of monitoring
  - Collect and assess ocular AEs related to product or procedure
  - Collect and assess AEs potentially related to gene therapy
Voretigene Neparvovec Clinical Perspective

Albert M. Maguire, MD
Professor of Ophthalmology
Perelman School of Medicine of the University of Pennsylvania
Patients with Biallelic \textit{RPE65} Mutation-Associated Retinal Dystrophy Eventually Progress to Complete Blindness

- No available treatments that slow or stop loss of functional vision and visual function
  - One device approved for end-stage RP
- Majority experience serious manifestations beginning in early childhood
  - Vision loss that substantially limits life activities
  - Affecting social, emotional, and physical well-being
- Progression continues throughout adulthood
Voretigene Established Clear Benefit – 1 Point Change Clinically Meaningful

- 93% score change ≥ 1
- Most patients became sure of themselves
  - Pushed aside guides
  - Explored environment independently and with confidence
  - Rarely relied on cane after treatment
- 1 light level changes are meaningful
  - Provide patients opportunity to gain or regain activities of daily living
1 Point Change Associated with Improvement in Functional Vision

- Full field light sensitivity
  - ~ 2 log / 100-fold improvement
  - Correlates with improved rod photoreceptor function
- Visual field
  - > 300 sum total degree improvement
Voretigene Provides Durable Improvement in Functional Vision
≥ 3 Years of Sustained Improvement

Bilateral Mobility Testing:
Baseline at 4 lux

Bilateral Mobility Testing:
Year 1 at 4 lux

Time to Completion: 129 seconds

Time to Completion: 23 seconds
Surgical Procedure
Summary of Surgical Experience

- By age 3, eye nearly 90% of adult size
  - No increased risk for surgical intervention
- Surgical results
  - Subretinal delivery of vector achieved in all cases
  - No retinotomy site complications
  - One intraoperative foveal dehiscence resolved early post-operative period
  - Outpatient procedure in Phase 3
  - Average operative time 1 hour
Favorable Safety Profile

- Up to 9 years post-administration follow-up
- Subretinal injection in each eye
  - Most AEs occur early and resolve over time
  - No repeat exposure to possible AEs
- Possibility of some decrease of visual acuity in some patients
- Most AEs related to surgical procedure
- Standardized administration procedure
Standardized Surgical Administration Technique Based on Clinical Program Experience

1. Conduct standard 3-port pars plana vitrectomy (Remove posterior cortex vitreous)

2. Select injection site
1. Conduct standard 3-port pars plana vitrectomy (Remove posterior cortex vitreous)
2. Select injection site
3. Inject voretigene in subretinal space
4. Perform fluid-air exchange
Risk of Surgical Complications Reduced By Using Well-Established Techniques

- Vitrectomy with pars plana instrumentation commonly performed by vitreoretinal surgeons
- Additional training to standardize subretinal injection part of Risk Management Plan
Voretigene Positive Benefit-Risk

- No available treatments that slow or stop loss of functional vision and visual function
- Voretigene provides clinically meaningful improvements
  - Prompt and durable regardless of extent of disease at diagnosis
- Manageable safety profile
Voretigene Neparvovec (Voretigene) for Confirmed Biallelic RPE65 Mutation-Associated Retinal Dystrophy

October 12, 2017
Spark Therapeutics
Cellular, Tissue and Gene Therapies Advisory Committee
Q&A SLIDES SHOWN ON SCREEN
Figure 18: Location of the Mutations in the RPE65 Gene in Patients Enrolled in Clinical Trials of Voretigene Neparvovec
Subjects with Bilateral MLMT Score Change of 1 Show Improvement in FST

MLMT Lux Score Bilateral Testing

Individual Patient Results

White Light Sensitivity ($\log_{10}$ cd.s/m²) (FST)

Individual Patient Results
Change at Year 1: MLMT Bilateral vs. FST Both Eyes, Correlation = -0.71
Phase 3: MLMT Lux Scores by Subject: 1st Eye

Original Intervention:
- 17 of 20 (85%) improved by ≥1 light level
- 10 of 20 (50%) achieved maximum LUX score
- 15 of 20 (75%) improved by ≥2 light levels

Control – After Treatment:
- 8 of 9 (89%) improved by ≥1 light level
- 7 of 9 (78%) achieved maximum LUX score
- 7 of 9 (78%) improved by ≥2 light levels

Individual Patient Results

BL Y1
- Original Intervention (N=20)
- Control/Intervention (N=9)
Phase 3: MLMT Lux Scores by Subject: 2nd Eye

Individual Patient Results

Original Intervention:
- 19 of 20 (95%) improved by ≥1 light level
- 12 of 20 (60%) achieved maximum LUX score
- 15 of 20 (75%) improved by ≥2 light levels

Control—After Treatment:
- 9 of 9 (100%) improved by ≥1 light level
- 8 of 9 (89%) achieved maximum LUX Score
- 6 of 9 (67%) improved by ≥2 light levels

BL Y1
○ Original Intervention (N=20) □ Control/Intervention (N=9)
Long-Term Follow-up in Phase 3 Patients Show Continued Improvements From Baseline Over Time

3-YEAR DATA NOT REVIEWED BY FDA
CO-112

MLMT Bilateral Lux Score for 4 Subjects with 4 Year Phase 3 Data, May 2017 Cutoff

Improvement

MLMT Lux Score Bilateral Testing

(1 lux) 6
(4 lux) 5
(10 lux) 4
(50 lux) 3
(125 lux) 2
(250 lux) 1
(400 lux) 0

Original Intervention (N=4)

Study Visit

Intervals are +/- 1 standard error

4-YEAR DATA NOT REVIEWED BY FDA
### 101 & 102 IFN-γ ELISPOT Assay Results for AAV Capsid and RPE65

<table>
<thead>
<tr>
<th>Subject</th>
<th>AAV Capsid Positive Result</th>
<th>RPE65 Positive Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH-13</td>
<td></td>
<td>Day 30</td>
</tr>
<tr>
<td>NP-15</td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Study 102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP-01</td>
<td>Day 90 (False Positive)</td>
<td>Week 5 (False Positive)</td>
</tr>
<tr>
<td>NP-04</td>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>CH-08</td>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>CH-09</td>
<td>Week 2</td>
<td></td>
</tr>
<tr>
<td>CH-10</td>
<td>Week 4 and Week 8</td>
<td>Week 8</td>
</tr>
<tr>
<td>CH-11</td>
<td></td>
<td>Week 6</td>
</tr>
</tbody>
</table>
At 1 Year Post Treatment 93% of Subjects Improved At Least One Light Level From Baseline (Phase 3)

Age at first injection is next to the Subject ID.
## Phase 3: Correlations Support Clinical Relevance of MLMT, Change at Year 1 Relative to Baseline

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>FST* Both Eyes</th>
<th>GVF III4e Both Eyes</th>
<th>Visual Acuity* (Holladay) Both Eyes</th>
<th>Visual Function Questionnaire (Subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLMT Bilateral Score Change</td>
<td>-0.71 (p &lt; 0.001)</td>
<td>0.64 (p &lt; 0.001)</td>
<td>-0.46 (p = 0.012)</td>
<td>0.46 (p = 0.011)</td>
</tr>
</tbody>
</table>

*Improvement in FST and VA are numerically characterized as decreases, thus the correlation is negative*

- Generally Good to Strong
- Generally Good
## MLMT Light Levels in Lux and Candela/m²

<table>
<thead>
<tr>
<th>Illuminance (lux)</th>
<th>Luminance (cd/m²)</th>
<th>Corresponding Example Environments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.32</td>
<td>Mesopic vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moonless summer night; or indoor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nightlight</td>
</tr>
<tr>
<td>4</td>
<td>1.30</td>
<td>Mesopic vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cloudless summer night with half</td>
</tr>
<tr>
<td></td>
<td></td>
<td>moon; or outdoor parking lot at</td>
</tr>
<tr>
<td></td>
<td></td>
<td>night</td>
</tr>
<tr>
<td>10</td>
<td>3.20</td>
<td>Mesopic vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 minutes after sunset in a city</td>
</tr>
<tr>
<td></td>
<td></td>
<td>setting; or a bus stop at night</td>
</tr>
<tr>
<td>50</td>
<td>15.9</td>
<td>Photopic vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Outdoor train station at night; or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>inside of illuminated office building stairwell</td>
</tr>
<tr>
<td>125</td>
<td>39.8</td>
<td>Photopic vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 minutes before sunrise; or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>interior of shopping mall, train,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or bus at night</td>
</tr>
<tr>
<td>250</td>
<td>79.6</td>
<td>Photopic vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interior of elevator, library, or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>office hallway</td>
</tr>
<tr>
<td>400</td>
<td>127.3</td>
<td>Photopic vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Office environment; or food court</td>
</tr>
</tbody>
</table>

National Institute of Standards and Technology-calibrated, Extech model #EA33 light meters used to provide examples and to set/verify specified light levels used for mobility testing; cd/m² = candela per square meter.

Data sources: Wyszecki and Stiles 1982 and adapted from Chung 2016.
## Phase 3: Comparison of Visual Acuity (Both Eyes) Modeled Results Using Holladay and Lange Scales (ITT)

<table>
<thead>
<tr>
<th>Visual Acuity – Both Eyes (ITT)</th>
<th>Difference (95% CI) [Intervention-Control]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holladay Scale</td>
<td>-0.16 (-0.41, 0.08)</td>
<td>0.17</td>
</tr>
<tr>
<td>Lange Scale</td>
<td>-0.16 (-0.31, -0.01)</td>
<td>0.035</td>
</tr>
</tbody>
</table>
# Phase 3: IFN-\(\gamma\) ELISPOT Assay Results for AAV2 Capsid and RPE65

<table>
<thead>
<tr>
<th>Patient</th>
<th>MLMT (\Delta) from Injection Baseline</th>
<th>Final lux Score</th>
<th>Age</th>
<th>RPE65 Gene Mutation</th>
<th>AAV2 Capsid Positive Result (SFU)</th>
<th>RPE65 Positive Result (SFU)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH-22</td>
<td>3</td>
<td>1</td>
<td>20</td>
<td>Leu341Ser</td>
<td>Baseline (55)</td>
<td>Year 1B (172)</td>
</tr>
<tr>
<td>IA-35</td>
<td>1</td>
<td>10</td>
<td>34</td>
<td>IVS1+5G&gt;A</td>
<td>Baseline (518)</td>
<td></td>
</tr>
<tr>
<td>CH-44</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>Arg44Gln / IVS7-2A&gt;C</td>
<td>Year 1B (170)</td>
<td></td>
</tr>
<tr>
<td><strong>Control/Intervention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH-17</td>
<td>5</td>
<td>1</td>
<td>20</td>
<td>Arg91Trp / Arg91Gln</td>
<td>Year 1C / Injection Baseline (375)</td>
<td></td>
</tr>
<tr>
<td>CH-18</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>Arg124Stop / Lys297delA</td>
<td></td>
<td>Year 1C / Injection Baseline (173)</td>
</tr>
<tr>
<td>CH-36</td>
<td>3</td>
<td>1</td>
<td>10</td>
<td>Arg44Gln</td>
<td></td>
<td>Baseline (402)</td>
</tr>
<tr>
<td>CH-37</td>
<td>1</td>
<td>1</td>
<td>25</td>
<td>Phe70Val / Tyr368His</td>
<td></td>
<td>Year 1C (298)</td>
</tr>
<tr>
<td>CH-43</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>Gly46delG</td>
<td></td>
<td>Year 1B (228)</td>
</tr>
</tbody>
</table>

Cutoff: AAV-2 50.0 SFU; RPE65 161.6 SFU
## FDA Table 15: Assessment of T-cell Immune Responses

<table>
<thead>
<tr>
<th>Tests</th>
<th>Study 101 (n=12)</th>
<th>Study 102 (n=11)</th>
<th>Study 301 (n=21)</th>
<th>Study 302 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human PBMC Interferon-γ Responses to AAV2 and RPE65 by ELISPOT at BL, Days 14, 30, and 90</td>
<td>No T cell response to AAV capsid and RPE65</td>
<td>Six subjects with low response at single time point</td>
<td>Two subjects with low response at single time point and one subject with medium response at single time point</td>
<td>Three subjects with low response (a), 1 subject with medium response (b), and 1 subject with high response (c)</td>
</tr>
</tbody>
</table>