Transformative RNA Based Treatments for Pulmonary Diseases

Corp. Update 2022

NON-CONFIDENTIAL
SpliSense – Pulmonary Diseases Focused Company

The Company

- Founded in 2017 by Prof. Batsheva Kerem (Hebrew University)
  - Part of the global team that cloned the CFTR gene
- Leadership team and advisors with strong track record in pulmonary development of inhaled therapies and ASOs

R&D Status

- Inhaled Antisense Oligonucleotides (ASOs)
  - High unmet need, orphan indications – Cystic Fibrosis
  - Larger, non orphan pulmonary indications - Muco- obstructive diseases
  - ASOs - clinically validated approach

Financial

- Backed by a strong syndicate including IBF, OrbiMed, Integra and CF Foundation
Antisense Oligonucleotides – Modulating RNA (MoA)

Gene

Transcription

Pre mRNA

Antisense Drug

SpliSense: Three MoA strategies

- Decreasing production of target proteins
- Restoring protein function
- Modulating RNA processing, (production of modified proteins)
SpliSense’s Platform Technology

Proprietary computational Algorithms for Splicing modulation and ASOs optimization

Robust genetic understanding of pulmonary diseases

Established combined inhaled Delivery system

Antisense Oligonucleotides - Modulating RNA
SpliSense’s Strategy from Orphan to Large Pulmonary Indications
### SpliSense’s Pulmonary Diverse Pipeline

<table>
<thead>
<tr>
<th>Indication</th>
<th>Approach</th>
<th>Program</th>
<th>Discovery</th>
<th>IND Enabling Studies</th>
<th>Clinical Studies</th>
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<tbody>
<tr>
<td><strong>Cystic Fibrosis</strong></td>
<td>Restoration of Protein Function</td>
<td>SPL84</td>
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<td>H2 2022</td>
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<td></td>
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<td>(3849 Mut.)</td>
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<td>Production of Modified Protein</td>
<td>SPL16</td>
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<td></td>
<td>SPL23</td>
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<td>(W1282X Mut.)</td>
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<td>SPL24</td>
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<td>(N1303K Mut.)</td>
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<tr>
<td><strong>Muco-Obstructive Diseases</strong></td>
<td>Decrease Production of Over-expressed Proteins</td>
<td>SPL5A</td>
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<td>2024</td>
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<tr>
<td>COPD, Asthma, Pulmonary Fibrosis</td>
<td></td>
<td>SPL5B</td>
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SpliSense Tackle Key Challenges of ASOs’ Delivery to Lungs
### SpliSense’s ASOs Have Unique Properties for Lung Delivery

<table>
<thead>
<tr>
<th>Natural</th>
<th>Durable</th>
<th>Precise</th>
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</thead>
<tbody>
<tr>
<td>➤ No vectors or delivery vehicles are needed</td>
<td>➤ Lungs $T_{1/2} \approx 2$ weeks</td>
<td>➤ Highly specific to target sequence</td>
</tr>
<tr>
<td>➤ Enable direct, non-invasive delivery</td>
<td>➤ Proven stability and Mucus penetration</td>
<td>➤ Minimal systemic exposure</td>
</tr>
<tr>
<td>➤ Lung cells uptake through endocytosis to:</td>
<td>➤ Proven stability in lysosomes extract and under acidic conditions</td>
<td>➤ Lung specific</td>
</tr>
<tr>
<td>➤ Epithelia cells</td>
<td>➤ End products are expected to be given to patients <strong>once a week or less</strong></td>
<td>➤ Proper Distribution in conducting airways</td>
</tr>
<tr>
<td>➤ Nucleus</td>
<td></td>
<td>➤ Clinically validated chemical modification patterns</td>
</tr>
</tbody>
</table>

**Natural**: No vectors or delivery vehicles are needed, enable direct, non-invasive delivery, lung cells uptake through endocytosis to: epithelia cells, nucleus.

**Durable**: Lungs $T_{1/2} \approx 2$ weeks, proven stability and mucus penetration, proven stability in lysosomes extract and under acidic conditions, end products are expected to be given to patients **once a week or less**.

**Precise**: Highly specific to target sequence, minimal systemic exposure, lung specific, proper distribution in conducting airways, clinically validated chemical modification patterns.
SpliSense’s ASOs Properly Distribute & Retained in WT and “Mucus Obstructive” Mice (β-ENaC) Lungs

Staining for SPL ASO following IT administration - dark staining
Comparable Distribution of SpliSense’ ASOs in WT and “Mucus Obstructive” (β-ENaC) Mice Lungs

24hrs post-dose

- β-ENaC
- WT

4 wk post-dose

- Trachea
- Bronchi
- Bronchioles
- Alveoli
SpliSense’s ASOs Can Be Detected in the Nucleus of Lung Epithelial Cells

Low and power (objective x10 and x100) microphotograph of lower-level bronchus and bronchiole section of beta ENaC mice lungs suggesting that SPL84-23 penetrates the target cells.
Cystic Fibrosis Programs
Cystic Fibrosis – Need for Novel Drugs

- A progressive, autosomal recessive genetic disease
- Caused by dysfunction of the CFTR transmembrane protein (chloride channel)
- Affects ~100,000 people worldwide
- The median predicted survival of people with CF is about 48 years
- Existing drugs alleviate symptoms but do not cure the disease
  - Suggesting that:
    - 33% of Trikafta® treated patients are not responding
    - 33% of Trikafta® treated patients have moderate response
- Lung transplantation is the only definitive treatment option for CF patients with end stage lung disease

“A third of the people clearly have a big response... Another third have an obvious response, but it may not be quite as dramatic... Another third, there isn’t as big a response...”

Peter Mogayz MD, Johns Hopkins School of Medicine

BofA Research, Feb 2022

“The Trikafta is an excellent drug – indeed ....However, it’s a band-aid, not a cure....... worries physicians, who predict that patients will be burdened by declining lung function .... eventually leading to substandard quality of life”

Josh Reshnik MD, RA Capital

*CF Foundation US survey – Feb 2022
SPL84
(Anti 3849 Mutation ASO)

Retains protein structure and activity
3849 Mutation – Unmet Need

TAM ~$450M

Kalydeco® FEV1 Effect < 2.7%.

Symdeko® FEV1 Effect <6%.

Annual Treatment Cost – $300k

No approved drug in EU

US CF Foundation Mission and Funding
During splicing, introns are removed, and exons are joined together producing the mRNA.

**ASO Technology Produce Mature and Functioning WT CFTR**

Oren et al. 2021
SPL84 Completely Restores CFTR Function in CF Patient Homozygote Derived Lung Cells (HBEs)

- **Ussing Assay is a Gold Standard for CF drugs efficacy assessment (FDA)**
- SPL84 **completely restores** CFTR function in 3849 patients derived Human Bronchial Epithelial Cells (HBEs)
- Symdeko® (tezacaftor/ivacaftor) has no effect on 3849 CF patient.
  - Strong correlation of Ussing analysis to clinical outcome
SPL84 Completely Restores CFTR Function in Heterozygous Patients’ Derived Cells

- Ussing Assay is a Gold Standard for CF drug efficacy assessment (FDA)
- SPL84 completely restores CFTR function in 3849 patient derived Human Nasal Epithelial Cells (HNEs) and Bronchial Epithelial Cells (HBEs)

SPL84 & Trikafta® have comparable & Synergic Effect in Heterozygous CF Patient Derived Lung Cells (HBEs)

- 50% of WT activity is the maximal effect in heterozygous patients. Synergic effect of combo. is observed.
- SPL84/ Trikafta® completely restores CFTR function in F508del/ 3849 patient derived Human Bronchial Epithelial Cells (HBEs)
Phase 1/2a Proposed Clinical Study Design To Be Initiated in H2 2022

**Part 1:**
**Single Ascending Dose (SAD) - HVs**
*n=32, 1:3 Placebo : ASO*

- 5 mg
- DSMB approval
- 10 mg
- DSMB approval
- 20 mg
- DSMB approval
- 40 mg

**Part 2:**
**Multiple Ascending Dose (MAD)**
**3849 subjects**
*n=38 1:3 Placebo: ASO 1 dose/week x 8 weeks*

- 5 mg
- 10 mg
- 20 mg
- 40 mg
- 40 mg EOW

DSMB data review on routine basis of all cohorts in Part 2

*Final doses will be selected based on tox. results*

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<thead>
<tr>
<th>Primary Objective</th>
<th>Assessment of safety and tolerability of inhaled SPL84-23-1</th>
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<tbody>
<tr>
<td>Secondary Objectives</td>
<td>To evaluate the change from baseline in laboratory parameters and vital signs</td>
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<tr>
<td>Exploratory Objectives</td>
<td>To measure the pharmacokinetics (PK) of SPL84-23-1 administered via inhalation</td>
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<tr>
<td>Exploratory Objectives</td>
<td>To explore the efficacy of ascending doses of SPL84-23-1 administered via inhalation (% change in FEV1 at 8 weeks)</td>
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# SPL84-23 Program (3849) Expedite Path To Approval

<table>
<thead>
<tr>
<th>Year</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
<th>2025</th>
<th>2026</th>
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<tr>
<td><strong>Regulatory</strong></td>
<td>US/EU ODD</td>
<td>Pre IND/SA</td>
<td>IND/CTA (Fast Track/PRIME?)</td>
<td>EOP2</td>
<td>Breakthrough?</td>
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<tr>
<td><strong>Pre-Clinical</strong></td>
<td>Tox studies</td>
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<td>Interim Analysis</td>
<td>Phase 1-2a</td>
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SPL23
(Anti W1282X Mutation ASO)

Modulates RNA processing and production of modified proteins
W1282X (Exon 23) Mutation – Unmet Need

TAM ~$550M

W1282X/non-F508del ~30yrs.

W1282X/non-F508del

No approved drug

Patient # Annual Growth 3.5%

Potential Expedite Regulatory path
W1282X Mutation - No CFTR Protein & No Activity

- No CFTR Protein or Activity

- Non-mature RNA

- Exon 22 >> Intron 22 >> Exon 23 >> Intron 23 >> Exon 24

- W1282X

- Splicing

- mRNA Lacking exon 23

- Functional CFTR Protein

- Control ASO SPL22
SPL23 Properly Restores CFTR Function in W1282X Patient Derived Nasal Cells

RNA- CFTR Exon 23 Skipping

Cont.  SPL23-2

CFTR chloride channel activity

Control ASO  SPL23

% of WT CFTR activity

Restoration of CFTR Function by Ussing

Homozygote W1282X

+TRIKAFTA®

Heterozygote W1282X/ non-F508del

+TRIKAFTA®

Potentially Translated to Significant Lung Function Improvement (~40% of HVs)
# SPL23-2 Program (W1282X) Clinical & Regulatory Road Map

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<th>2022</th>
<th>2023</th>
<th>2024</th>
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<td><strong>Regulatory</strong></td>
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Expanding SpliSense Platform Technology from Orphan to Large Pulmonary Indications
Muco-Obstructive Diseases
Mucin Lowering ASO (SPL5)

Decrease production of over-expressed proteins
Mucus Hypersecretion is a Clinical Feature of Severe Respiratory Diseases

- Mucus- The first line of innate defense against inhaled pathogens and particles in the respiratory tract is airway mucus
  - Mucus layer comprised of approximately 98% water, 2% solids (mostly mucins)
- MUC5AC, MUC5B are predominate mucins secreted in the lungs and polymerize to form gels
  - In muco-obstructive diseases mucins content increases to 5-9%
- Mucus and mucins are generated by goblet cells
- Excessive mucus drives:
  - Respiratory infections
  - Respiratory air blockage
  - Respiratory disease worsening

Roy et al. 2014, Roy et al. 2019, Ridley et al. 2018
Muco-Obstructive Lung Disease Progression
SPL5 Lowers RNA and Protein Expression (MoA)

**Gene**

**Transcription**

**Pre-mRNA**

**mRNA**

Exon skipping leading to PTC (premature stop codon)

**Export**

**Cytoplasm**

Translation of truncated protein and NMD activation

Reduction in protein levels
PoC Mucin Lowering ASO: Lungs Goblets Cells Distribution & Mucin Lowering Activity

Hybridization signal at the of goblet cells (Beta ENaC/WT mice)

Black staining - SPL ASO
Blue\Purple staining- Mucus in goblet cells

A549 Human Lung Cancer Cells
SpliSense ASOs Approach: Platform Technology for Precises Pulmonary Therapies

- Pulmonary focused company
- Robust inhalation approach
- Proper penetration, migration and stability in mucus
- Diverse pipeline, orphan & large unmet indications
- 1st program, clinical study H2 2022
- 2nd program, aiming for accelerated approval

Mastering protein production & expression in a targeted manner.
Management & Leadership Team

Gili Hart PhD - CEO
Biotech executive with extensive experience in global drug development from pre-clinical through successful Phase 3 trials. Former CEO of Mitoconix Bio and OPKO Biologics.

Batsheva Kerem PhD - Co-founder & CSO
Prof. Hebrew University of Jerusalem. 30 years of leading research in CF genetics starting with the discovery of the CFTR gene.

Oren Gez, MBA - CBO
An experienced and appreciated financer with over 18 years of experience in the global capital market working at local and international investment banking.

Efrat Ozeri-Galai PhD - VP Research
Extensive experience in CF and pulmonary diseases genetics, discovery and pre-clinical development.

Asaf Cohen, B.Sc, MBA - VP CMC
Vast experience in CMC worlds, focusing on production, analytical and device development under GMP regulatory environments.

Nissim Darvish, M.D., Ph.D. - Chairman
Managing General Partner at MeOhr Ventures
Former Director at Orbimed Advisors LLC and Orbimed Israel Partners. Spent 8 years prior with Pitango Venture Capital

Prof. Eitan Kerem MD - CMO
Pediatric pulmonologist; Head of the Pediatric Pulmonology Unit of HMC Jerusalem, Chairman of the Israeli CF Foundation CAB.

Asaf Cohen, B.Sc, MBA - VP CMC
Vast experience in CMC worlds, focusing on production, analytical and device development under GMP regulatory environments.
Investment Opportunity - 2022 Financial Round

- Splisense is seeking to raise $40M to support 2023-24 expenses including:
  - Advancing additional pre-clinical programs into the clinic (IND)
    - SPL23 (Anti W1282X Mutation ASO)
    - SPL16/SPL24
    - Advancing Mucins lowering ASOs to IND
      - MUC5AC
      - MUC5B
SpliSense Value Inflection Points 2022-2024

### SPL84-23-1 (CF)
- **2022**
  - **H1**: Pre IND/SA
  - **H2**: Fast Track/PRIME
- **2023**
  - **H1**: IND/CTA submission
  - **H2**: Phase I interim analysis
- **2024**
  - **H1**: Breakthrough
  - **H2**: PHIII

### SPL23-2 (CF)
- **2022**
  - **H1**: US/EU ODD
  - **H2**: Pre IND/SA
- **2023**
  - **H1**: Tox data
  - **H2**: Fast Track/PRIME IND/CTA submission
- **2024**
  - **H1**: Phase I interim analysis
  - **H2**: acc/con. approval

### SPL5A/B (COPD/Asthma)
- **2022**
  - **H1**: In-vitro Poc
  - **H2**: In-Vivo Poc
- **2023**
  - **H1**: Tox data
  - **H2**: Pre IND
- **2024**
  - **H1**: IND/CTA submission
  - **H2**: PHIII

**Timeline:**
- 2022
- 2023
- 2024

**Value Inflection Points:**
- 2022-2024
Thank You!