Transformative RNA Based Treatments for CF & Pulmonary Diseases

Corp. Update 2021

NON-CONFIDENTIAL
SpliSense – CF & 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
- Based in Jerusalem, Israel

R&D Status

- Inhaled Antisense Oligonucleotides (ASOs)
  - Initial focus on high unmet need, orphan indications (CF)
  - Subsequent expansion to larger, non orphan pulmonary indications (muco-obstructive diseases)
  - ASOs - clinically validated approach
  - Two clinical programs to be initiated in late 2022

Financial

- Backed by a strong syndicate including: OrbiMed, CF Foundation, IBF and Integra (VC arm of Hebrew University)
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.

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

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

**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
SpliSense’s Proprietary computational Algorithms for Splicing modulation and ASOs optimization

Robust genetic understanding of pulmonary diseases

Established combined inhaled Delivery system

Antisense Oligonucleotides- Modulating RNA
Antisense Oligonucleotides – Modulating RNA (MoA)

Gene → mRNA → Antisense Drug

MoA: Three possible approaches

- Decreasing production of target proteins
- Restoring protein function
- Modulating RNA processing, (production of modified proteins)
SpliSense Approach – Splicing Modulation of mRNA

Pre-mRNA Splicing

Exon Intron Exon Intron

Alternatively spliced mRNAs

Translation

Protein Isoforms

Cytoplasm

Nucleus

ASO
## SpliSense’s CF & Pulmonary Diverse Pipeline

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<td>Restoration of Protein Function</td>
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<td>Production of Modified Protein</td>
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<td>Muco-Obstructive Diseases</td>
<td>Decrease Production of Over-expressed Proteins</td>
<td>SPL23-2</td>
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<td>SPL5A/B</td>
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(COPD, PCD, CF, Asthma, Pulmonary Fibrosis etc.)
SpliSense ASOs Designed for Proper Delivery to Lungs
Use of Inhaled Delivery of ASOs for Lung Diseases

- ASOs are chemically modified for stability and increased lung cells uptake
  - No vectors or delivery vehicles are needed
  - Shown to penetrate the cells via endocytosis efficiently
- Enables direct non-invasive delivery even of high doses (highly soluble) with minimal systemic exposure
- ASOs for inhalation:
  - Infrastructure for inhalation is established and commercially available
  - Stable post nebulization
- SpliSense end products are expected to be given to patients once a week or less, thus reducing patients’ treatment burden
SpliSense ASOs are Stable in Hyper-Concentrated Mucus, and Properly Migrate Through it

SPL ASO is stable in patients' mucus

SPL ASO properly migrates through viscous mucus
SpliSense’s ASOs Properly Distribute & Are Retained in WT and “Mucus Obstructive” Mice Lungs (β-ENaC Mice Model)

Staining for SPL84-23-1 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

1wk post-dose

WT

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 – Unmet Need

- A progressive, life shortening autosomal recessive genetic disease due to **dysfunction of the CFTR** transmembrane protein – chloride channel

- Affects ~90,000 people worldwide (80% with F508del mutation)

- The median predicted survival of people with CF is about 39 years
  - Unless carrying the F508del mutation (Trikafta®)

- Existing drugs alleviate symptoms but do not cure the disease
  - Lung transplantation is the only definitive treatment option for CF patients with end stage lung disease

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SPL84-23
(Anti 3849 Mutation ASO)
Retains protein structure and activity
3849 Mutation – Unmet Need

Patient population
~1300
(Annual Growth 3%)

Annual Treatment Cost – $300k

Kalydeco® FEV1
Effect < 2.7%.

No approved drug in EU

Symdeko® FEV1
Effect <6%.

US CF Foundation Mission and Funding
ASO Technology Produce Mature and Functioning WT CFTR

During splicing, introns are removed, and exons are joined together producing the mRNA.

Non-mature RNA

mRNA

Oren et al. 2021
SPL84-23 Completely Restores CFTR Function in Patients Derived Cells (50% of WT- Ussing Assay)

- **Ussing Assay is a Gold Standard for CF drugs efficacy assessment (FDA)**
- SPL84-23 completely restore CFTR function in 3849 patients derived Human Nasal Epithelial Cells (HNEs)
- SPL84-23 completely restore CFTR function in 3849 patients derived Bronchi Epithelial Cells (HBEs)

Average of HNEs from 5 patients carrying the 3849 mutation*

Average 50% of WT

HBEs from a patient (3849/F508del)*

Average 50% of WT

CFTR chloride channel activity

Control ASO
SPL84-23

ΔIsc CFTRinh172 (μA/cm²)

0 10 20 30 40 50 60

0 2 4 6 8 10 12 14

% of WT (ΔIscCFTRinh172)

Control ASO
SPL84-23

Phase 1/2a Proposed Clinical Study Design To Be Initiated in H2 2022

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

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

DSMB approval

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

**Part 2:**
**Multiple Ascending Dose (MAD)**
n=36, 1:3 Placebo: ASO
1 dose/week x 8 weeks

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

DSMB approval

DSMB approval

DSMB approval

*Final doses will be selected based on tox. results

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<th>Primary Objective</th>
<th>Secondary Objectives</th>
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<td>Assessment of safety and tolerability of inhaled SPL84-23-1</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>
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<th>Year</th>
<th>Regulatory</th>
<th>Pre- Clinical</th>
<th>Clinical</th>
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<td>NDA Submission</td>
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<td>Registrational P3 Study</td>
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- US/EU ODD
- Pre IND/SA
- IND
- EOP2
- Fast track/ Breakthrough
- Study start up
- Interim Analysis
- NDA Submission
- Registrational P3 Study
SPL23-2
(Anti W1282X Mutation ASO)

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

Patient population ~1000

W1282X/non-F508del patients - no approved drug

Patient # Annual Growth 3.5%

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

Non-mature RNA

mRNA with the W1282X mutation

Splicing

No CFTR Protein or Activity

Functional CFTR Protein

Splicing

mRNA lacking exon 23

ASO

Control ASO

VX445(1µM) VX661(3µM)

α-CFTR (596)

α-Calnexin 95

CFTX WT

Band C

Band B

VX445(1µM) VX661(3µM)

Control SPL23-2

VX445(1µM) VX661(3µM)

α-CFTR (596)

α-Calnexin 95

CFTX WT

Band C'

Band B'
SPL232 Properly Restores CFTR Function in W1282X Patient Derived Cells (36% of WT- Ussing Assay)

Dose Dependent Exon 23 Skipping (RNA level)

Restoration of CFTR Function by Ussing

Control ASO
SPL23-2
0
1
2
3
4
5
6
ΔIscCFTRinh172 (µA/cm²)
+TRIKAFTA

CFTR chloride channel activity

SPL232 Properly Restores CFTR Function in W1282X Patient Derived Cells (36% of WT- Ussing Assay)
SPL23-2 Program (W1282x) Clinical & Regulatory Road Map

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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
  - Pathogenesis of numerous respiratory diseases
  - Respiratory air blockage

Roy et al. 2014, Roy et al. 2019, Ridley et al. 2018
Muco-Obstructive Lung Disease Progression

Normal

Muco-Obstruction

Chronic

Mucin
Fluid

CF
COPD
PCD
Asthma
IPF
MUC5AB and MUC5C are Dominate Players in Pulmonary Diseases Progression and Severity

- MUC5AC and MUC5B levels are higher in **COPD patients (3rd leading cause of death by disease in US)**
  - In COPD sputum, both MUC5AC and MUC5B protein levels are significantly increased
  - Levels of MUC5B and MUC5AC in current/ former smokers with severe COPD were approx. 3X and 10X higher, respectively, than non-smokers
  - MUC5B overproduction correlates with an increase in disease severity and decreased lung function

- **In Asthma**, MUC5AC levels are significantly increased
- Total mucin concentrations in **CF sputum** are elevated as compared to healthy control subjects
- Chronic overexpression of MUC5B, driven by single base mutation, is the single greatest risk factor for the development of **Idiopathic Pulmonary Fibrosis (IPF)**

Mucins Excessive Production in Patients with Pulmonary Diseases

Healthy Persons (N=69)

Patients with COPD (N=359)

Patients with NCFB (N=99)

Patients with CF (N=20)

Patients with PCD (N=42)

Large Market Potential

Boucher RC et al. 2019
SPL5 Lowers RNA and Protein Expression (MoA)

Gene

Pre-mRNA

Antisense Drug

Exon skipping leading to PTC (premature stop codon)

mRNA

Export

Reduction in protein levels

Cytoplasm

Translation of truncated protein and NMD activation

Gene

Transcription

Pre-mRNA

mRNA

STOP

Export

mRNA

STOP

Reduction in protein levels

Cytoplasm

Translation of truncated protein and NMD activation

Gene

Transcription

Pre-mRNA

mRNA

STOP

Export

mRNA

STOP

Reduction in protein levels

Cytoplasm

Translation of truncated protein and NMD activation
PoC Mucin Lowering ASO: Lungs Goblets Cells Distribution and In Vitro Activity

Hybridization signal at the apical part of goblet cells (Beta ENaC mice)
- Black staining - SPL ASO
- Blue staining – Mucus in goblet cells

A549 Cells
Lung Cancer Cells
Splisense is a **pulmonary focused company** using ASO technology to modulate RNA, and thus mastering protein production and expression in a specific and targeted manner.

- clinically validated technology

- **Proper penetration, migration and stability in Mucus**

- Established and robust inhalation approach (lung distribution, cellular penetration, inhalation device, safety assessment)

- **Diverse pipeline**
  - Large market potential
    - Initial focus on high unmet need, orphan indications (CF) Subsequent expansion to larger, non orphan pulmonary indications (muco- obstructive diseases)
  - 2 programs in IND enabling phase; 2 **clinical studies to commence in 2022**

- **1st program, SPL84-23, fully funded up to phase 1-2 study completion (CF Foundation)**
Thank You!