ESCAPE Develops Precisely Targeted Novel Therapies for Genetically Defined Neurodegenerative Diseases

- **Diverse pipeline** focused on genetically defined neurodegenerative diseases
- **Selective therapies** that overcome liabilities of non-selective approaches

- Clinical stage, selective S1P5 agonist and near-clinical, selective G2019S LRRK2 program and early state APOE4 program
Diversified Pipeline of Precisely Targeted, Novel Small Molecules

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>INDICATION</th>
<th>PATIENT SELECTION</th>
<th>DISCOVERY</th>
<th>IND ENABLING</th>
<th>PHASE 1 SAD / MAD</th>
<th>PHASE 1b/2a BIOMARKERS</th>
<th>ANTICIPATED MILESTONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESB1609 S1P5 Selective Agonist</td>
<td>Lysosomal Storage Disorders</td>
<td>Niemann-Pick Type C</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>MAD in Process</td>
</tr>
<tr>
<td></td>
<td>Parkinson’s Disease</td>
<td>GBA PD</td>
<td>[ ]</td>
<td>[ ]</td>
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<td>[ ]</td>
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<tr>
<td>ESB5070 G2019S LRRK2 Kinase Inhibitor</td>
<td>Parkinson’s Disease</td>
<td>LRRK2 G2019S Carriers</td>
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<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>IND</td>
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<td>Structure Modulator of ApoE4</td>
<td>Alzheimer’s Disease</td>
<td>ApoE4 Carriers</td>
<td>[ ]</td>
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<td>[ ]</td>
<td>[ ]</td>
<td>Development Candidate</td>
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</table>

ESCAPE BIO
ESB1609: S1P5
Selective Agonist
ESCAPE’s S1P5 Selective Agonists Avoid the Limitations of Approved Non-selective Modulators

<table>
<thead>
<tr>
<th>Indication</th>
<th>Phase</th>
<th>S1P5</th>
<th>S1P1</th>
<th>S1P3</th>
<th>S1P4</th>
<th>Adverse Event Profile</th>
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<tbody>
<tr>
<td><strong>S1P5 Selective Agonists</strong></td>
<td></td>
<td></td>
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<tr>
<td>ESB1609</td>
<td>NPC, others</td>
<td>Phase I</td>
<td></td>
<td></td>
<td></td>
<td>• No immune, CV or hepatotoxicity observed preclinically</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• S1P5 primarily expressed in CNS</td>
</tr>
<tr>
<td><strong>Non-Selective Modulators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRMS</td>
<td>Approved</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Peripheral immune suppression</td>
</tr>
<tr>
<td>Mayzent</td>
<td>SPMS</td>
<td>Approved</td>
<td></td>
<td></td>
<td></td>
<td>• Bradycardia, AV block, blood pressure alteration</td>
</tr>
<tr>
<td>Zeposia</td>
<td>RRMS</td>
<td>Approved</td>
<td></td>
<td></td>
<td></td>
<td>• Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Bronchoconstriction</td>
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<tr>
<td>Ponesimod</td>
<td>MS</td>
<td>Phase 3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Amiselimod</td>
<td>MS, Crohns</td>
<td>Phase 2</td>
<td></td>
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</table>

**NPC:** Niemann-Pick Type C; **MS:** multiple sclerosis; **RRMS:** relapsing-remitting multiple sclerosis; **SPMS:** secondary progressive multiple sclerosis
Lysosomal Dysfunction is a Common Pathogenic Driver in Genetically Defined Neurodegenerative Diseases

- **PATHOGENIC MUTATION**
  - Lysosomal enzyme deficiencies
  - Altered lipid homeostasis

- **Lysosomal** Dysfunction
  - Lipid Dysmetabolism
  - Neuronal & Glial cell dysfunction & inflammation
  - Proteinopathies; Aggregation Aβ, α-synuclein, tau, mHTT

- **DISEASE**
  - Neurodegeneration
# S1P5 Agonism Consistently Restores Markers of Lysosomal Dysfunction, Neurodegeneration & Neurological Function

<table>
<thead>
<tr>
<th>Disease</th>
<th>Model</th>
<th>Improved Brain Lipid Levels</th>
<th>Improved Neurodegenerative Biomarkers</th>
<th>Neurological Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged Rodent</td>
<td>WT</td>
<td>+++</td>
<td><em>Explored in disease models</em></td>
<td>+++</td>
</tr>
<tr>
<td>Senescence accelerated (age and dementia)</td>
<td>SAMP8</td>
<td>+++</td>
<td>↓ Aβ</td>
<td>+++</td>
</tr>
<tr>
<td>Alzheimer’s Disease (amyloid / tauopathy)</td>
<td>Tg2576 / P301S</td>
<td>+++</td>
<td>↓ Aβ / ↓ Tau</td>
<td>+++</td>
</tr>
<tr>
<td>Niemann-Pick C Disease</td>
<td>BALB/cNctr-Npc1m1N/J</td>
<td>+++</td>
<td>↑ CSF Aβ, Tau and pTau ↓ Aβ</td>
<td>+++</td>
</tr>
<tr>
<td>Parkinson’s Disease</td>
<td>A53T Synuclein</td>
<td>In process</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Huntington’s Disease</td>
<td>R6/2</td>
<td><em>Not reported</em></td>
<td>↓ mutant Htt</td>
<td>+++</td>
</tr>
</tbody>
</table>
S1P5 Agonism Improves Lysosomal & Neurodegenerative Biomarkers and Neurological Function in NPC* Null Mice

**Lysosomal NPC Biomarkers**

- **CNS ceramide C18**
  - Untreated mice expected to have decreased ceramide levels.
  - S1P5 agonism reverses trend in a dose-proportional manner.

- **CNS S1P levels**
  - Treated mice show increased S1P levels.

**Neurodegenerative Biomarkers**

- **Amyloid β 1-40 (Soluble)**
  - Untreated mice have decreased soluble amyloid β levels.
  - S1P5 agonism reverses trend in a dose-proportional manner.

**Neurological Function**

- **Grip Strength**
  - Improved in treated mice compared to untreated.

- **Dystonic Features Score**
  - Lower scores in treated mice.

*NPC BALB/cNctr-Npc1m1N/J
Data from S1P5 agonist AV432

One-way ANOVA, post-hoc Dunnett
* P < 0.05, ** P < 0.01
ESB1609: A Potent & Brain Penetrant S1P5 Selective Agonist with Excellent Clinical Safety and Tolerability

Strong CNS product profile:
- Highly potent and 1,000 fold selective for S1P5
- Excellent brain penetration (Brain/Plasma ratio 0.8)
- Oral, once daily dosing with durable CNS exposure (CSF)

Excellent safety & tolerability

Manufacturing: Small molecule process; GMP batches produced

Intellectual Property: Broad patent estate; coverage into 2030’s

Clinical: Ph1 multiple-ascending dose underway → P1b 2020

Regulatory: Discussions ongoing for orphan indications
ESB1609: Dose Dependent, Prolonged and Consistent Cerebral Spinal Fluid (CSF) Exposure in Single-Ascending Oral Dose Healthy Volunteer Phase 1 Study

P1, Randomized, Placebo-Controlled, Safety, Tolerability and PK Single Ascending Dose Study of ESB1609 in Healthy Volunteers with a Continuous CSF Sampling Cohort

48 hr Plasma Concentration (ug/mL)

24 hr CSF Concentration (nM)

73nM approximate EC50, 210nM 3x EC50 anticipated for clinical efficacy
MAD Study Design and Overview of Objectives

**Part 1: Healthy Volunteers (HVs)**

- **Cohort 1**
  - ESB1609 (n=6) or Placebo (n=3)
  - Safety, PK

- **Cohort 2**
  - ESB1609 (n=6) or Placebo (n=3)

- **Cohort 3A**
  - ESB1609 (n=4) or Placebo (n=4)
  - Safety, PK (Plasma and CSF)
  - CSF Biomarkers (BMs) in HVs

- **Cohort 3B CSF**
  - ESB1609 (n=3) or Placebo (n=3)

**Part 2: NPC Subjects**

- **Cohort 4**
  - ESB1609 (n=8) or Placebo (n=4)
  - Safety, PK (Plasma and CSF)
  - CSF BMs in placebo and treated NPC subjects to assess BM noise, variability in placebo
  - Time course of BMs in NPC subjects
  - Gain experience in sample handling to translate to associated diseases of lipid dyshomeostasis (e.g. GBA PD)

- **Open label extension**
ESB5070: G2019S Mutant LRRK2 Kinase Inhibitor
LRRK2 is a Compelling Therapeutic Target for Genetic Parkinson’s Disease

- G2019S is most common LRRK2 pathogenic mutation, 1-3% of all PD
- Majority of patients with G2019S LRRK2 PD carry only 1 copy of the mutation, the second copy is normal
- Normal LRRK2 acts on downstream Rab GTPases, which orchestrate critical biological functions
- G2019S mutation elevates kinase activity via autophosphorylation at pS1292
- Program goal is to inhibit pathogenic hyperphosphorylated kinase activity from G2019S mutation and spare normal LRRK2 function
- Ideal opportunity for precision medicine by targeting only G2019S LRRK2
ESCAPE Precisely Targets the Pathogenic Activity of G2019S LRRK2

- Denali, Biogen (ASO) & others inhibit BOTH mutant and wild type LRRK2 equally (non-selective)
- Strong non-selective inhibition of LRRK2 produces pulmonary and renal histopathology similar to severe human pulmonary disease (e.g. pulmonary fibrosis, ARDS, COPD, vaping related lung injury)
- Denali targeting 50% pS935 inhibition at trough to avoid safety concern, potentially compromising efficacy

Non-Selective On-Target Safety Limitation

- High ATP-competitive inhibition of LRRK2
  - Renal and pulmonary histopathological toxicity
  - Reversible, but not monitorable
- Knockout/kinase dead TG mice show tox
  - One wild type copy rescues toxicity

Selective Inhibition Maximizes G2019S Inhibition Sparing WT LRRK2 Function
ESCAPE Demonstrates G2019S Specific Inhibition Ex Vivo Sparing Healthy LRRK2 in Parkinson’s Patient Blood Cells

• **G2019S-selective inhibitor**
  – Inhibited ~90% of pS935 & pRab10 in homozygous G2019S carriers
  – Only ~10% inhibition in non-carriers
  – 100x selective tool compound

• **Compared to non-selective inhibitor**
  – Equal high inhibition across genotypes

PBMCs were isolated from whole blood and treated ex-vivo with tool molecules
3 HOM G2019S-LRRK2, 5 HET G2019S-LRRK2, 5 non-carriers
ESCAPE Has Developed Potent, Mutant Selective and Brain Penetrant LRRK2 Inhibitors from Multiple Chemical Series

- Screened ~800K compounds from 3 diverse libraries
- Evolved a single HTS hit into 4 distinct, G2019S-selective, proprietary chemical series
- Potency of compounds down to pM levels and selectivity > 1000-fold
- Series follow iterative development of novel compounds combining good potency, selectivity, brain uptake, and bioavailability
- Distinct chemotypes expanded to encompass 4 COM patents pending, 1 published

41126 Series
- 1st patent

42500 Series
- 2nd patent

42156 Series
- 3rd patent

44846 Series
- 4th patent
ESB5070 is a Potent, Brain-Penetrant G2019S Selective LRRK2 Inhibitor

<table>
<thead>
<tr>
<th>Feature</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dosing, with bid - tid frequency</td>
<td>✓</td>
</tr>
<tr>
<td>Potency on G2019S LRRK2 (IC$_{50}$ pS935, pS1292 in HEK/GS cells &lt;50 nM)</td>
<td>✓</td>
</tr>
<tr>
<td>Cellular Selectivity on G2019S LRRK2 &gt; WT LRRK2 &gt;100X</td>
<td>✓</td>
</tr>
<tr>
<td>Pharmacokinetics: Target coverage inhibition in brain without lung tox</td>
<td>✓</td>
</tr>
<tr>
<td>Safety: Clean on safety screens, no histopath findings in tox studies</td>
<td>✓</td>
</tr>
<tr>
<td>Intellectual Property: Multiple COM patents on novo small molecules</td>
<td>✓</td>
</tr>
</tbody>
</table>
## Predicted pS935 Inhibition in Lung and Histopathological Phenotype

<table>
<thead>
<tr>
<th>LRRK2 Inhibitor</th>
<th>HOM G2019S Lung (IC90 dose)</th>
<th>HET G2019S Lung (HOM IC90 dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100x G2019S-selective</td>
<td>90% inhibition</td>
<td>50% inhibition</td>
</tr>
<tr>
<td></td>
<td>Vacuolization</td>
<td>No vacuolization</td>
</tr>
<tr>
<td>Non-selective (MLi-2)</td>
<td>90% inhibition</td>
<td>90% inhibition</td>
</tr>
<tr>
<td></td>
<td>Vacuolization</td>
<td>Vacuolization</td>
</tr>
</tbody>
</table>

### Lung Safety POC Study Goals

- Demonstrate that sustained IC90 inhibition of G2019S-LRRK2 in brain in heterozygous G2019S KI mice does not induce on-target vacuolization in lung that is characteristic of non-selective inhibitors
- Establish relationship between inhibition of pharmacodynamic markers and on-target lung vacuolization
ESCAPE Compounds Achieve Strong Pathogenic Inhibition of G2019S Activity in HET Mice Brain **Without** Inducing On Target Lung Histopathology

• 100 mg/kg BID EB-45070 inhibited pS935 in brain by 45-69% throughout the day while brain pS1292 (autophosphorylation site) was inhibited 90-97%, suggesting selective inhibition of G2019S-LRRK2
• As predicted, the 100 mg/kg BID dose did not induce vacuolization in lung

### HET G2019S KI (N = 8 mice per group)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>EB-45070 LOW DOSE BID</th>
<th>EB-45070 HIGH DOSE BID</th>
<th>MLI2 60 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pS935</strong> % inhibition at plasma Cmin vs Cmax</td>
<td>0%</td>
<td>45 - 69%</td>
<td>80 - 86%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>pS1292</strong> % inhibition at plasma Cmin vs Cmax</td>
<td>0%</td>
<td>90 - 97%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table shows inhibition of pS935/total-LRRK2 and pS1292/total-LRRK2
*Inhibition at Cmin was extrapolated from PK model and concentration-response curve generated from PK/PD studies performed at Cmax

Histopath Scale
- Absent
- Minimal
- Mild
- Moderate
- Marked
- Severe

Lung Vacuolization

100 mg/kg BID EB-45070 inhibited pS935 in brain by 45-69% throughout the day while brain pS1292 (autophosphorylation site) was inhibited 90-97%, suggesting selective inhibition of G2019S-LRRK2

As predicted, the 100 mg/kg BID dose did not induce vacuolization in lung
Building a LRRK2 Biomarker Platform Relevant to Genetic Population

**Actions:**

- Enrich the CSF domain with additional pathway engagement assays (EFFICACY)
  - Denali working on lysosome measures in clinical Ph1 studies with their non-selective molecules (JPM + Cowen)
  - Exploit mitochondrial, lysosome, lipid & neuroinflammation markers for linkage to G2019S LRRK2
- Rationalize a multi-modal (imaging, digital, fluids) longitudinal exploratory observational study

<table>
<thead>
<tr>
<th>MOUSE</th>
</tr>
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<tbody>
<tr>
<td><strong>G2019S Knock In</strong></td>
</tr>
<tr>
<td><strong>PK</strong></td>
</tr>
<tr>
<td><strong>PD</strong></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>HUMAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G2019S carriers</strong></td>
</tr>
<tr>
<td><strong>PK</strong></td>
</tr>
<tr>
<td><strong>PD</strong></td>
</tr>
</tbody>
</table>

**PET Biodistribution**
ESB5070: First-in-Class G2019S Selective LRRK2 Inhibitor

Highly potent small molecules

Precisely targeted to G2019S LRRK2 kinase activity

Multiple COMs filed; 1 published

Multiple chemical scaffold series backups

DC EB-45070 is:
- Brain penetrant
- With acceptable ADME & safety screen profile
- No adverse findings in non-GLP toxicology studies
- Dose ranging PK/PD, CMC & safety studies ongoing to enable Ph 1

2nd generation compounds in late safety screening
G2019S Selective Inhibitor Market Sizing
Analyst Reports Indicate Blockbuster Opportunity

- **Large Orphan**: 20,000 – 30,000 patients in U.S.
- **Smaller Orphan**: $3 - $4B LRRK2 U.S. Market Opportunity

**Market Size**

**E.U. Market Opportunity**: 20,000 – 30,000 patients in U.S.

**Greater Genetic Testing**

**Treatment of Presymptomatic Patient Population**

Note: market opportunities not drawn to scale
## Robust Pipeline of Precisely Targeted, Novel CNS Therapies

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>INDICATION</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
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<tbody>
<tr>
<td>ESB1609 S1P5 Selective Agonist</td>
<td>Niemann-Pick Type C</td>
<td>IND-Enabling</td>
<td>Ph1 SAD</td>
<td>Ph1 MAD</td>
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<tr>
<td></td>
<td>GBA Parkinson’s Disease</td>
<td>Ph1b NPC OLE</td>
<td>Ph 2/3</td>
<td>Ph 1 PK/PD</td>
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<tr>
<td>ESB5070 LRRK2 Kinase Inhibitor</td>
<td>Parkinson’s Disease (G2019S Carriers)</td>
<td>DC</td>
<td>IND-Enabling</td>
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<td>Structure Modulator of ApoE4</td>
<td>Alzheimer’s Disease</td>
<td>DC</td>
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<td>DC</td>
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<table>
<thead>
<tr>
<th>Use of Proceeds Period:</th>
<th>Series A</th>
<th>Series B</th>
<th>Series C / Crossover</th>
</tr>
</thead>
</table>

*DC = Clinical Development Candidate Nomination*
Experienced Leadership Team & Strong Investors

EXECUTIVE MANAGEMENT

Julie Anne Smith
President & CEO

Carrolee Barlow, MD
Chief Medical Officer

Paul Wren, PhD
Chief Scientific Officer

Tony Rimac
Chief Financial Officer

Jacob Schwarz, PhD
Head of Chemistry

INVESTOR SYNDICATE

OrbiMed
Healthcare Fund Management

SUTTER HILL VENTURES

Lilly Asia Ventures

Abbvie