Disclaimers

Forward Looking Statements
This presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation, including without limitation statements regarding future results of operations and financial position of Denali Therapeutics Inc. (“Denali” or the “Company”), business strategy, business plans, product candidates, planned preclinical studies and clinical trials, expectations regarding the timing of results of such studies and trials, plans and expectations regarding patient recruitment, planned regulatory filings, long-term development plans and near-term pipeline milestones, Company priorities, regulatory approvals, timing and likelihood of success and expectations regarding collaborations, are forward-looking statements. Denali has based these forward-looking statements largely on its current expectations and projections about future events. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including but not limited to, risks related to: Denali’s early stages of clinical drug development; Denali’s ability to complete the development of, and if approved, commercialization of its product candidates; Denali’s dependence on successful development of its BBB platform technology, product candidates currently in its core program and biomarker strategy; expectations and potential benefits of strategic collaboration agreements and Denali’s ability to attract collaborators with development, regulatory and commercialization expertise; the risk that a transaction or collaboration may not close in a timely manner or at all, and the ability to obtain any requisite regulatory approvals related to such transaction or collaboration; Denali’s ability to conduct or complete clinical trials on expected timelines; the uncertainty that any of Denali’s product candidates will receive regulatory approval necessary to be commercialized; Denali’s ability to obtain and maintain regulatory approval of its product candidates, and any related restrictions, limitations and/or warnings in the label of any approved product candidate; Denali’s ability to continue to create a pipeline of product candidates and develop commercially successful products; Denali’s ability to obtain, maintain, or protect intellectual property rights related to its product candidates and BBB platform technology; implementation of Denali’s strategic plans for its business, product candidates and BBB platform technology; Denali’s ability to obtain funding for its operations, including funding necessary to develop and commercialize its product candidates; and other risks. In light of these risks, uncertainties and assumptions, the forward-looking statements and events discussed in this presentation are inherently uncertain and may not occur, and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Accordingly, you should not rely upon forward-looking statements as predictions of future events. Information regarding additional risks and uncertainties may be found in Denali’s Annual Report on Form 10-K filed with the SEC on March 12, 2019, Denali’s Quarterly Report on Form 10-Q filed with the SEC on May 8, 2019 and Denali’s future reports to be filed with the SEC. Denali does not undertake any obligation to update or revise any forward-looking statements, to conform these statements to actual results or to make changes in Denali’s expectations, except as required by law.

Accuracy of Data
This presentation contains statistical data based on independent industry publications or other publicly available information, as well as other information based on Denali’s internal sources. Denali has not independently verified the accuracy or completeness of the data contained in these industry publications and other publicly available information. Accordingly, Denali makes no representations as to the accuracy or completeness of that data.
RECENT BUSINESS HIGHLIGHTS

**LRRK2i**
- Parkinson’s
  - Initiated Phase 1b study in Parkinson’s patients with DNL201 (+/- LRRK2 mutation)
  - Continued progress in Phase 1 HV study with DNL151

**RIPK1i**
- ALS, AD, MS & others
  - Partnership with Sanofi for global development and commercialization
  - Initiated Phase 1b study in Alzheimer’s patients (lead: Denali)
  - Initiated Phase 1b study in ALS patients (lead: Sanofi)

**ETV:IDS**
- MPS II (Hunter Syndrome)
  - Established PoC Hunter Syndrome disease model in mice and nonhuman primates
  - Initiated cell line development for ETV:IDS (DNL310) and on track for IND filing in 2019

**Pipeline & Partnerships**
- Advanced early stage pipeline with potential for 3-4 additional INDs in 2019-2020
- Established/expanded partnerships with F-star, AbCellera, Sirion, Centogene and others
- Partnership with Takeda for three TV Platform programs for global development and commercialization
DENALI’S APPROACH TO DEFEAT NEURODEGENERATION

Three R&D Principles
- Genetic Pathway Potential
- Engineering Brain Delivery
- Biomarker-Driven Development

Three Business Principles
- Broad Portfolio
- Parallel Investments
- Strategic Partnering

INCREASED PROBABILITY OF SUCCESS
DEGENOGENES DEFINE NEURODEGENERATION BIOLOGY
NEW GENETIC INSIGHTS OPEN UP NEW THERAPEUTIC TARGETS AND PATHWAYS

Alzheimer's Disease

- APP
- PSEN1
- APOE4
- PSEN2

Parkinson's Disease

- SNCA
- PARK2
- PARK7

ALS / FTD

- SOD1
- MAPT
- ALS2

Number of Genetic Associations and Implicated Genes

Alzheimer's Disease:
- 0
- APP
- PSEN1
- APOE4
- PSEN2

Parkinson's Disease:
- 58
- SNCA
- PARK2
- PARK7

ALS / FTD:
- 45
- SOD1
- MAPT
- ALS2

Gliai Biology-related Degenogenes
Lysosomal Function-related Degenogenes
Cellular Homeostasis-related Degenogenes
Other Degenogenes

DEGENOGENES

Alzheimer's Disease

- APP
- PSEN1
- APOE4
- PSEN2

Parkinson's Disease

- SNCA
- PARK2
- PARK7

ALS / FTD

- SOD1
- MAPT
- ALS2

DEGENOGENES DEFINE NEURODEGENERATION BIOLOGY
NEW GENETIC INSIGHTS OPEN UP NEW THERAPEUTIC TARGETS AND PATHWAYS

Gliai Biology-related Degenogenes
Lysosomal Function-related Degenogenes
Cellular Homeostasis-related Degenogenes
Other Degenogenes

DEGENOGENES

Alzheimer's Disease

- APP
- PSEN1
- APOE4
- PSEN2

Parkinson's Disease

- SNCA
- PARK2
- PARK7

ALS / FTD

- SOD1
- MAPT
- ALS2
THE BLOOD-BRAIN BARRIER (BBB) CHALLENGE

- The blood-brain barrier evolved to protect the central nervous system and maintain a homeostatic environment in the brain.
- Tight junctions, efflux pumps, and transporters regulate access of substances to the brain.
- Achieving therapeutically relevant drug concentrations in the brain has been a major challenge.
**TWO PLATFORMS: BIOLOGY & BLOOD-BRAIN BARRIER TECHNOLOGY TECHNOLOGY**

### BIOLOGY PLATFORM

- **Genetic Pathway Potential**
  - DEGENOGENES

### BBB TECHNOLOGY PLATFORM

- **Engineering Brain Delivery**

#### Biology Focus Areas

- **LYSOSOMAL FUNCTION**
  - LRRK2
  - ETV:IDS
  - RIPK1
  - ATV:TREM2
  - ATV:Tau
  - Undisclosed

- **GLIAL BIOLOGY**
  - ATV:aSyn
  - Undisclosed

- **CELLULAR HOMEOSTASIS**
  - Undisclosed

- **OTHER TV-ENABLED APPROACHES**
  - Undisclosed

#### Denali Programs

- **Small Molecule**
- **Large Molecule (TV)**
BIOMARKER-DRIVEN DEVELOPMENT PRINCIPLES

**Target Engagement**
Determine the relationship between dose and drug response

**Pathway Engagement**
Demonstrate an effect on Pathway Biology

**Patient Phenotyping**
Intersection of Pathway Biology & Disease Biology

INCREASED PROBABILITY OF PHASE 2 AND 3 SUCCESS
<table>
<thead>
<tr>
<th>Program Target</th>
<th>Drug Candidate</th>
<th>Disease Indication</th>
<th>Drug Development</th>
<th>Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lyssosomal Function Pathway</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LRRK2</td>
<td>DNL201 LEAD</td>
<td>Parkinson’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DNL151</td>
<td>Parkinson’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iduronate 2-sulfatase</td>
<td>DNL310</td>
<td>MPS II (Hunter Syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-Synuclein</td>
<td>ATV:aSyn</td>
<td>Parkinson’s, DLB, MSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td>LF1</td>
<td>Neurodegeneration</td>
<td></td>
<td>Takeda</td>
</tr>
<tr>
<td><strong>Glial Biology Pathway</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIPK1 (CNS)</td>
<td>DNL747</td>
<td>Alzheimer’s, ALS, MS</td>
<td></td>
<td>Sanofi</td>
</tr>
<tr>
<td>TREM2</td>
<td>ATV:TREM2</td>
<td>Alzheimer’s</td>
<td></td>
<td>Takeda</td>
</tr>
<tr>
<td>Undisclosed</td>
<td>GB1</td>
<td>Alzheimer’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cellular Homeostasis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau</td>
<td>ATV: Tau</td>
<td>Alzheimer’s</td>
<td></td>
<td>Takeda</td>
</tr>
<tr>
<td>Undisclosed</td>
<td>CH1</td>
<td>Neurodegeneration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td>CH2</td>
<td>Alzheimer’s, ALS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td>CH3</td>
<td>ALS, Parkinson’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIPK1 (Peripheral)</td>
<td>DNL758</td>
<td>RA, Psoriasis</td>
<td></td>
<td>Sanofi</td>
</tr>
<tr>
<td>Undisclosed</td>
<td>OT1</td>
<td>Undisclosed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td>OT2</td>
<td>Undisclosed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ENGINEERING SMALL MOLECULES TO CROSS THE BBB

Denali Therapeutics data from DNL201 Human Phase 1 study
LRRK2 PROGRAM
LRRK2 INHIBITION IMPROVESLYSOSOMAL FUNCTION

- Lysosomal dysfunction is a central pathology of Parkinson’s and leads to protein aggregation (aSyn in Lewy bodies) and death of dopaminergic neurons
- LRRK2 activity is increased in Parkinson’s disease
- LRRK2 is a negative regulator of lysosomal function
- LRRK2 inhibition rescues lysosomal function and normalizes protein processing
• PK profile supports twice daily dosing
• Terminal half life of 14-26 hours
• Low to moderate variability in Cmax and AUC
• Steady state reached by Day 10

• Mean CSF to unbound plasma ratio of ~1.0
• Data from 25, 80 and 100 mg BID multiple dose cohorts
DNL201 DOSE-DEPENDENT INHIBITION OF LRRK2 IN PHASE 1 (HV)

- Time course of LRRK2 pS935 inhibition after DNL201 administration every 12 hours until day 10
RIPK1 PROGRAM
RIPK1 REGULATES INFLAMMATION AND NECROPTOSIS

- Microglial dysfunction contributes to neurodegeneration in Alzheimer’s and other chronic neurodegenerative diseases

- RIPK1 kinase activation is increased neurodegenerative diseases, including ALS and AD, and generates a pro-inflammatory response in microglia and cell death via necroptosis in other cell types

- RIPK1 inhibition enables selective inhibition of the TNFR1 pathway and regulates the production of pro-inflammatory cytokines and necroptosis in the brain
DNL747 PHARMACOKINETIC PROPERTIES AND BRAIN EXPOSURE

- Well behaved PK profile
- Terminal half life of 12 hours across dose levels
- Low to moderate variability in Cmax and AUC

- Mean CSF to unbound plasma ratio of 1.51 ± 0.23
- Data from all multiple dose cohorts
DNL747 DOSE-DEPENDENT INHIBITION OF RIPK1 IN HEALTHY SUBJECTS

- Time course of RIPK1 pS166 inhibition after DNL747 administration every 12 hours until day 14
TV PLATFORM
POOR BRAIN EXPOSURE DIMINISHES LIKELIHOOD OF SUCCESS FOR BIOTHERAPEUTICS FOR NEURODEGENERATIVE DISEASES

10mg/kg i.v. antibody dose

C_{max}(serum) = 1.3 \mu M

C_{max}(brain) mAb = \sim 1nM (insufficient for therapeutic effect)

C_{max}(brain) ATV = \sim 20nM (in therapeutic range for most targets)

Enhanced ATV brain exposure increases extent of target engagement and improves potential for successful treatment of neurodegeneration

Low mAb exposure limits target engagement (\leq 20%)

Higher ATV exposure drives full target engagement (\geq 94%)

0.01nM target affinity
1nM target affinity

[target] = 5nM

\leq 20% 20x

\geq 94%
THE TRANSPORT VEHICLE (TV) BLOOD BRAIN BARRIER PLATFORM

**Modular platform technology to deliver protein therapeutics to the brain**

- BBB receptor (TfR) binding integrated into IgG Fc
- Retains stability and pharmacokinetics of IgG
- Modular platform to transport antibodies and other proteins

**Established proof of concept in nonhuman primates**

- 30x Brain Concentration
- Sustained PD Effect
- 20-30x increased exposure and broad distribution in brain
- Sustained pharmacodynamic effect for 10+ days
- Established PK and safety profile for clinical development
HUNTER SYNDROME (MPSII)

PATHOGENESIS
• Inherited Lysosomal Storage Disease caused by mutations in the IDS gene encoding iduronate-2-sulfatase

PATIENTS
• X-linked recessive disorder – males only
• Initial presentation at age 1-3 years
• Progressive cognitive, language, and motor decline

TREATMENT
• Enzyme replacement therapy approved for somatic symptoms (Elaprase®; Shire):
  - >10 years of clinical experience; weekly IV infusions
  - Provides clinical benefit for somatic symptoms, but no benefit for CNS symptoms
• No approved therapy for neurological manifestations

• ETV:IDS (DNL310) will be IV delivered and is intended to treat both peripheral and CNS manifestations of MPSII
ETV:IDS ROBUSTLY REDUCES GAGS IN THE PERIPHERY AND BRAIN

**Liver GAGs**

**Spleen GAGs**

**Brain GAGs**

**CSF GAGs**

*ETV:IDS has superior effect to IDS in the brain and equivalent effect in peripheral organs*

*n=8 per IDS KO; TIR^mu hu group or 5 per TIR^mu hu group, data shown as mean ± s.e.m.; *** p < 0.001, **** p < 0.0001; ns = not significant*
ETV:IDS CORRECTS DOWNSTREAM PATHWAY DYSFUNCTION

DNL310 corrects secondary lysosomal lipid accumulation

Brain Gangliosides

![Graph showing brain gangliosides levels](image1)

Brain BMP

![Graph showing brain BMP levels](image2)

ETV:IDS CORRECTS DOWNSTREAM PATHOLOGY, INCLUDING LYSOSOMAL LIPID STORAGE AND MICROGLIAL ACTIVATION

DNL310 corrects elevated Trem2 levels in brain

Brain TREM2

![Graph showing brain Trem2 levels](image3)

n=8 per IDS KO; TIR<sup>mu</sup>/hu group or 5 per TIR<sup>mu</sup>/hu group, data shown as mean ± s.e.m.; *** p < 0.001 and **** p < 0.0001
### Clinical Development Overview

<table>
<thead>
<tr>
<th>LRRK2</th>
<th>RIPK1</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNL201 Phase 1b (LRRK2+ / IPD)</td>
<td>DNL747 Phase 1b (ALS)</td>
</tr>
<tr>
<td></td>
<td>DNL747 Phase 1b (AD)</td>
</tr>
<tr>
<td></td>
<td>DNL747 Phase 2 (MS)</td>
</tr>
<tr>
<td></td>
<td>DNL747 Phase 2 Biomarker (AD)</td>
</tr>
<tr>
<td></td>
<td>DNL747 Phase 2/3 (ALS)</td>
</tr>
<tr>
<td></td>
<td>DNL747 Phase 2/3 (ALS)</td>
</tr>
<tr>
<td>Phase 2/3 (LRRK2+)</td>
<td>Phase 2/3 (IPD)</td>
</tr>
<tr>
<td>Phase 2 Imaging Study (LRRK2+)</td>
<td>Phase 2/3 (IPD)</td>
</tr>
<tr>
<td>YE 2019</td>
<td>YE 2019</td>
</tr>
</tbody>
</table>

**ETV:IDS**

- DNL310 Phase 1/2 (Hunter Syndrome)
- YE 2019

**Led by Sanofi**

**IND Filing**

**Data**
## DENALI PORTFOLIO: STATUS AND MILESTONES 2018 TO 2020

<table>
<thead>
<tr>
<th>Program</th>
<th>IND</th>
<th>Ph 1 HV Data</th>
<th>Patient Biomarker Data</th>
<th>Initiate Ph 2 or Ph 3 Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRRK2 (DNL201)</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(DNL151)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIPK1 (DNL747)</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALS, Alzheimer’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETV:IDS (DNL310)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional 3-4 INDs planned in the next 12-24 months

DELIVERING CLINICAL DATA AND MOVING TO PIVOTAL TRIALS
THANK YOU