SCD and CNS: creating breakthrough treatments harnessing the power of soluble guanylate cyclase (sGC)
Safe Harbor Statement

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Applicable risks and uncertainties include those listed under the heading “Risk Factors” and elsewhere in our most recent Form 10-K filed with the SEC on March 12, 2020, and in our subsequent SEC filings, including our Quarterly Report on Form 10-Q filed with the SEC on May 4, 2020. These forward-looking statements speak only as of the date of this presentation, and we undertake no obligation and do not intend to update these forward-looking statements.
Creating value from pioneering approaches to SCD and CNS

Two priority disease areas creating multiple potential ways to win in sickle cell and CNS

- genetically and phenotypically defined populations with high unmet need
- harness power, signaling precision of sGC
- biomarker-guided fast-to-POC trials underway
- supported by discovery platform
- attractive to investors and partners

Innovative sGC platform for the NO-sGC-cGMP pathway

- multi-dimensional pharmacology well-suited to disease biology
- molecules tailored to the tissues relevant to the disease
- wholly owned IP
- validated class

Building a company: our sGC science, pipeline and our team
Clinical program snapshot

**Ph1 (n=86 HV) SAD/MAD**
- Q2 2019
- Safety/tolerability
- Target engagement
- QD dosing

**Ph1b translational pharmacology study**
- December 2019
- Safety/tolerability
- Target engagement
- QD dosing
- CNS penetration

**Ph2 STRONG-SCD study in SCD**
- Top line expected late Q3 2020
- Safety, tolerability, PK
- Target and pathway engagement
- Pharmacodynamic effect: biomarkers (Hb, HbF, inflammation, adhesion) and daily symptoms

**Ph 3 study: SCD**

**Ph 2a study: Alzheimer’s disease with vascular pathology (ADv)**
- Top line expected late summer 2020
- Safety/tolerability in elderly subjects
- PK
- Target and pathway engagement
- Pharmacodynamic biomarkers: CBF, cGMP

Lessons inform iterative development strategy

Cyclerion
Olinciguat: potential to raise the standard of care for sickle cell disease patients

- potential for broad clinical utility in SCD
- multi-dimensional mechanism that offers both upstream and downstream pharmacology
- 70 patients enrolled; dosing completed
- TL expected late Q3 2020
- Ph3 long-lead items underway: CMC, protocols, global ad board, regulatory plans
- plan to develop and commercialize ourselves, but partnerships will be considered
Potential for broad clinical utility

- Newly approved therapies each target a single clinical domain...
- …olinciguat has the potential to improve four daily symptoms and end-organ protection remain unaddressed, decreasing QoL and increasing mortality
- Further improvement in anemia and/or VOC possible with olinciguat alone or as add-on therapy serving broad SCD patient population
Olinciguat: potential upstream and downstream interventions

Increased hemolysis leads to reduced nitric oxide state

sGC stimulation may restore deficient nitric oxide signaling

Upstream
• increased HbF may lead to reduced proportion of sickled RBCs

Downstream
• improved blood flow
• decreased vascular inflammation & cell adhesion
• improved endothelial integrity

Preclinical data support clinical investigation

**INFLAMMATION**

- Decrease in progression of hemolytic anemia in Townes SCD mouse model
  - Lower levels of vascular inflammatory markers and improved vascular function in mouse models of inflammation

**ANEMIA**

- Total hemoglobin
  - Decrease in progression of hemolytic anemia in Townes SCD mouse model

**FETAL HEMOGLOBIN**

- Higher mRNA expression of the γ-globin subunit of fetal hemoglobin in cultured cells

**SURVIVAL**

- Olinciguat extended survival in TNFα challenge Berkeley SCD mouse model

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Adhesion can occlude microcirculation and lead to painful VOC and other serious complications; 1. **** p<0.0001 vs TNFα-vehicle, 1h predose olinciguat followed by treatment with TNFα in normal mice; 2.*p<0.05; 3. **** p<0.0001 vs vehicle Treatment of K562 cells with vehicle or olinciguat for 7 days in cell culture, 4 * p<0.05 vs TNFα-vehicle, work done collaboratively with the laboratory of Paul Frenette (Albert Einstein), HU did not show benefit to survival
1h predose olinciguat followed by treatment with TNFα in preclinical model†

† in models of vascular inflammation, * p<0.05, ** p<0.001; **** p<0.0001 vs TNFα-vehicle
In a preclinical model of SCD, progression of hemolytic anemia was ameliorated in olinciguat treated Townes mice.
Olinciguat decreased biomarkers of inflammation, endothelial activation and renal injury in Townes SCD mice after 8 weeks of treatment

*\(p<0.05\), **\(p<0.01\), ***\(p<0.001\)
Olinciguat Phase 1: target engagement, PK, safety, QD dosing

Phase 1 design
- 5 Ph1 studies including:
  - SAD
  - MAD
  - clinical pharmacology
- 125 healthy volunteers
- age range 18-57
- standard safety
- PK
- 8 dose levels tested

Results
- linear, predictable PK; consistent with QD dosing
- determined well tolerated dose range
- evidence of target engagement and proof of pharmacology (cGMP elevation, blood pressure)
- well tolerated at all dose levels, no safety signals or discontinuations due to drug-related adverse events (AE)
- balanced tissue: plasma distribution

*Based on positive CNS pharmacology in multiple preclinical models
Structure
- 70 patients enrolled in all SCD genotypes, aged 16 – 70
- placebo controlled, double blind
- 4 dose levels
- 12-week treatment

Objectives
- assess safety and tolerability
- confirm PK profile in SCD patients
- development of the CYCN fit-for-purpose patient-reported outcomes (ePRO) instrument
- signs of pharmacodynamic effect: biomarkers (Hb, HbF, inflammation, adheion) and daily symptom effects

Insights for Phase 3 design
- endpoint selection based on results (biomarkers and ePRO)
- determine study sample size and dose(s)
Our strategy: target identifiable populations with important unmet needs

- targeting the untapped NO neurotransmitter pathway by sGC stimulation
- initial two indications are characterized by strong biological rationale, targeted patient populations, enormous unmet patient need, lack of approved therapies, and biomarker-based development

- MELAS
  - genetically defined rare disease
  - most common mitochondrial disease, >90% have neurological symptoms (stroke-like episodes, dementia, epilepsy, vision loss)
  - identifiable patients with no approved treatment

- Alzheimer's disease with vascular pathology (ADv)
  - intersection of Alzheimer's and vascular dementias
  - well-defined subset of patients, ~2M patients in the US
  - no approved therapies to treat vascular pathology of Alzheimer's disease

- discovery research engine focused on expanding CNS platform
- exploring R&D collaboration to support pursuit of the best opportunities
Our approach: intersection of patients and biology

Raising the odds of success:

• pursue multiple indications in parallel
• leverage biomarkers to drive development
• implement nimble trials with leading edge investigators and imaging analytics
• investigate a strategic R&D partnership to explore full potential of sGC in the CNS
sGC stimulators: potential to be next druggable neurotransmitter system

Successfully drugged neurotransmitter systems

**GABAergic**
- Valium® (1963)
- Ambien® (1992)

**Dopaminergic**
- Levodopa (1970)
- Risperdal® (1993)

**Adrenergic/Serotonergic**
- Amitriptyline (1961)
- Prozac® (1987)
- Paxil® (1992)

**Cholinergic**
- Scopolamine (1979)
- Aricept® (1996)

**Glutamatergic**
- Ketamine (1970)

**Nitric oxide**
- IW-6463
IW-6463 demonstrates in preclinical studies beneficial effects in four important domains of neurodegenerative diseases

<table>
<thead>
<tr>
<th>IMPROVE</th>
<th>ENHANCE</th>
<th>REDUCE</th>
<th>IMPROVE</th>
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<tbody>
<tr>
<td>Cerebral Blood Flow</td>
<td>Cellular Bioenergetics</td>
<td>Neuro-inflammation</td>
<td>Neuronal Function</td>
</tr>
<tr>
<td>Increased blood flow in areas associated with memory and arousal by fMRI BOLD imaging</td>
<td>Increased ATP and restored gene expression in cells from patients with mitochondrial diseases</td>
<td>Decreased markers of LPS-induced neuroinflammation (ICAM1, VCAM1, IL6) in vitro</td>
<td>Enhanced memory performance &amp; spine density in aged animals; increased LTP in neurodegenerative disease models</td>
</tr>
</tbody>
</table>
IW-6463 preclinical results support potential broad use in CNS treatment

**IMPROVE**
- Cerebral Blood Flow

**ENHANCE**
- Cellular Bioenergetics

**REDUCE**
- Neuro-inflammation

**IMPROVE**
- Neuronal Function

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**Mitochondrial disease patient cells**

**Inflammatory cytokine in rat brain 3D microtissues**

**Maze performance in aged rats**

- Aged rat/Vehicle
- Aged rat/IW-6463
Translational approach from discovery to approval and beyond

- Establish PD biomarkers preclinically
  Effects across four domains of neurodegenerative disease

- Validate PD biomarkers in the clinic
  Translational pharmacology study in elderly

- Refine clinical strategy
  - indication selection
  - patient selection
  - biomarker enrichment
  - endpoint selection
  - trial design
  - regulatory approach

- Smaller/shorter studies
  Evaluate IW-6463 in focused patient populations
  Initial approvals based on predictive surrogate and/or symptomatic and functional endpoints

- Larger/longer studies
  Evaluate IW-6463’s full potential
  Potential to expand label to broader populations and to demonstrate disease modification

Top line data late summer 2020
Biomarker-driven IW-6463 early clinical development strategy

**CNS exposure**
- safety
- pharmacokinetics
- pharmacodynamics
- target engagement
- dose selection for next study

**Phase 1** (completed)
- safety
- pharmacokinetics
- pharmacodynamics
- target engagement
- dose selection for next study

**Translational pharmacology study in elderly (ongoing)**
- safety
- pharmacokinetics
- target engagement
- pharmacodynamic biomarkers

**CNS activity**
- top-line expected late summer 2020

**Parallel exploratory Phase 2 studies**
- focused patient subsets
- translational biomarker data
- safety
- pharmacokinetics
- pharmacodynamics
- early impact on disease

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Phase 1 studies conducted at Centre for Human Drug Research, Leiden, NL
IW-6463 Phase 1: CNS exposure, target engagement, PK, and safety

PHASE 1 (completed)

Study design
- three stages:
  - SAD
  - MAD
  - food interaction
- 110 healthy volunteers
- age range 18-63
- standard safety
- PK (blood & CSF)
- wide dose range tested

Results
- identified safe and well-tolerated dose levels with steady-state CNS exposure in therapeutic target range*
- linear, predictable PK; consistent with QD dosing
- CNS exposure confirmed
- evidence of target engagement (blood pressure)
- well tolerated at all dose levels, no safety signals
- may be taken with or without food

*Based on positive CNS pharmacology in multiple preclinical models
Translational study design: pharmacodynamic biomarkers and safety

24 elderly subjects

IW-6463 QD

placebo

washout

placebo

IW-6463 QD

15 days

Assessing safety, PK and target engagement in CNS (cGMP)

Top line data expected late summer 2020

**IMPROVE**

**Cerebral Blood Flow**

- MRI arterial spin labeling (ASL)

**ENHANCE**

**Cellular Bioenergetics**

- brain metabolism via magnetic resonance spectroscopy (MRS)

**REDUCE**

**Neuro-inflammation**

- cytokines, adhesion molecules

**IMPROVE**

**Neuronal Function**

- qEEG
- measures of cognition and behavior (NeuroCart®)
Mitochondrial Encephalomyopathy, Lactic Acidosis, & Stroke-like Episodes (MELAS) genetically defined orphan disease, serious CNS & multi-system problems, no approved treatments

SYMPTOM OVERVIEW

Central Nervous system
Strokes, Stroke-like Episodes (SLEs), Ataxia (Imbalance), Epilepsy (Seizures), Migraine, Headaches, Cognitive Impairment, Learning Disability, Dementia, Mood disorders

Autonomic Nervous System
Dysautonomia, Temperature Intolerance, Heart Rate Instability (POTS)

Peripheral Nervous System
Peripheral Neuropathy

Skeletal muscle
Muscle weakness, myopathy, exercise intolerance

Vision
Vision Loss, Cortical Blindness, Ptosis, Ophthalmoplegia, Retinal-Optic Nerve Disease

Hearing
Sensorineural Hearing Loss, Tinnitus

Cardiac
Sudden Death, Arrhythmias, Cardiomyopathy

Gastrointestinal
Vomiting, Pseudoobstruction

Endocrine/Metabolic
Diabetes Mellitus, Short Stature, Underweight, Fatigue, Lactic Acidosis

Renal
Nephropathy
MELAS: Strong supportive data for NO-sGC-cGMP pathway involvement

**Scientific rationale for indication and patient selection**

<table>
<thead>
<tr>
<th>Clinical precedence for NO-sGC-cGMP pathway</th>
<th>Pathophysiology</th>
<th>IW-6463 pharmacology</th>
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<tbody>
<tr>
<td>• L-Arginine (NO precursor) recommended for acute and chronic treatment</td>
<td>• CNS metabolic dysfunction, elevated lactate, decreased NO</td>
<td>• CYCN preclinical data suggest IW-6463 improves mitochondrial function and cerebral blood flow</td>
</tr>
<tr>
<td></td>
<td>• CNS vascular pathology - impaired blood flow, inflammation, endothelial dysfunction, small vessel disease</td>
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Ph 2a: open-label study of IW-6463 in patients with MELAS

Enrichment strategy
- genetically defined MELAS with neurological features and elevated plasma lactate (disease biomarker)

Treatment
- once-daily IW-6463
- 29 days
- up to 20 patients (targeting 12 completers)

Sites
- centers of excellence for mitochondrial diseases: CHOP, MGH, Children’s National, Columbia, Hopkins

Objectives
- evaluate safety, tolerability, and pharmacodynamics
- assess near-term impact on disease-specific biomarkers
- de-risk and accelerate future development

DISEASE DOMAIN ASSESSMENT

Mitochondrial dysfunction
- Lactate

Dysregulated brain perfusion
- Cerebral Blood Flow (MRI ASL)

Neurodegeneration
- NF-L

Cognitive impairment
- Cognitive and behavior tests

Improved lactate and CBF would indicate an impact on the underlying disease mechanism and suggest potential for broad benefit for these patients.
AD with vascular pathology (ADv) – focused mixed dementia subset
Defined population well suited for treatment with IW-6463

DISEASE RATIONALE FOR PATIENT SELECTION

Pathophysiology
NO dysregulation, endothelial cell loss, impaired blood flow, vascular leakage, inflammation, neuronal dysfunction, and neuronal loss are major contributing factors to rapid disease progression

Standard of care
No approved therapies to treat vascular dementia. AD therapies offer limited benefits; not disease modifying

Pharmacology
Our preclinical data suggests IW-6463 has potential to improve cerebral blood flow, endothelial health, neuroinflammation, and cellular energetics as well as prevent neurodegeneration

Target population
ADv: an identifiable subset of mixed dementia patients with:
• AD pathology AND
• sub-cortical vascular disease AND
• CV risk factors
Ph 2a study of IW-6463 in ADv: emerging design

**STUDY START 1H 2021**

**Treatment**
- once-daily IW-6463

**Enrichment strategy**
- confirmed AD pathology (PET, CSF)
- 3+ cardiovascular risk factors
- mild-moderate subcortical small-vessel disease on MRI
- mini Mental State Exam score (16-26)

**Objectives**
- establish safety and pharmacodynamic effects of IW-6463 in a short-term study
- de-risk progression to larger, longer symptomatic and disease modification trials

**DISEASE DOMAIN**

**ASSESSMENT**

<table>
<thead>
<tr>
<th>Disease Domain</th>
<th>Assessment</th>
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<tr>
<td>Vascular dysfunction</td>
<td>ASL (CBF)</td>
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<tr>
<td>Neurodegeneration</td>
<td>neurofilament light chain</td>
</tr>
<tr>
<td>Neuroinflammation</td>
<td>vascular cell adhesion molecule</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
<td>N-acetyl aspartate (MRS)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>cognitive and behavior tests</td>
</tr>
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*Improved CBF, particularly in the context of memory improvements, would indicate an impact on the underlying disease mechanism and enable a targeted design for the next development stage.*
Building our company: the science, the pipeline and the team

- sGC stimulators: powerful intervention in a genetically and clinically validated pathway
- a wholly owned pipeline of differentiated molecules
- exploring partnerships across programs; praliciguat out-licensing scope expanded
- experienced leadership team with a distinctive track record of innovative drug discovery and development
- starting Q3 2020 with ~$61M cash*; supports our priorities into second half of 2021
- limited disruption from Covid-19

* Preliminary, unaudited unrestricted cash, cash equivalents and restricted cash balance as of June 30, 2020
sGC stimulators: ideal intervention in a genetically and clinically validated pathway

- multiple successful drugs target the NO-sGC-cGMP pathway for the treatment of CV diseases
  NO donors, PDE inhibitors, sGC stimulators

- NO-sGC-cGMP pathway plays central role in CNS diseases
  Network analysis delivers z-scores for CNS diseases similar to validated CV diseases

- sGC: optimal target for pathway intervention
  Broadly expressed in CNS, amplifies endogenous signaling, increases cGMP levels at the source with no attenuation of response
Broad impact in the NO-sGC-cGMP pathway

Evolution of understanding of impact of NO-sGC-cGMP pathway

- Smooth Muscle & Vascular Function
- Inflammation
- Metabolism
- Cellular Bioenergetics
- Neuronal Function
sGC stimulators are positive allosteric modulators that enhance NO-sGC-cGMP signaling
## A wholly owned pipeline of differentiated molecules

<table>
<thead>
<tr>
<th>Completed Clinical POC</th>
<th>Ongoing Clinical Programs</th>
<th>Preclinical</th>
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<tr>
<td><strong>Praliciguat</strong></td>
<td><strong>Olinciguat</strong></td>
<td><strong>Liver-targeted</strong></td>
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</table>
| Results support out-license for further development | Phase 2 proof-of-concept study in sickle cell disease ongoing (SCD)  
Topline data expected late Q3 2020 | IW-6463  
Phase 1 completed, with good CNS exposure, once-daily oral PK, and good safety/tolerability.  
Translational pharmacology study dosing completed; top line data expected late summer 2020 | Lung-targeted  
Anticipate launching two exploratory Phase 2 studies |

IW-6463
Praliciguat out-licensing discussions ongoing with expanded scope

Data support further development

- promising DN results:
  - UACR reductions on top of standard of care
  - reductions in blood pressure, HbA1c, total and LDL cholesterol
  - favorable safety profile, consistent with previous studies
  - attractive dosing and PK relative to others in class

- VICTORIA results further validate cardiometabolic potential of the class and suggest potential for praliciguat as a cardio metabolic therapeutic

Out-licensing discussions ongoing

- continuing discussions to out-license global rights to praliciguat
- expanded the scope of its out-licensing discussions beyond cardiometabolic disorders to include additional indications where sGC stimulators have shown efficacy
- no assurances on the prospects or timing of any partnership or licensing transactions--generally or specifically on praliciguat
Experienced team and successful leadership

• distinctive track record of innovative drug discovery/development (e.g.--CELEBREX®, KALYDECO®, LINZESS®, LUNESTA®, OPDIVO®, ORKAMBI®, YERVOY®)

• successful sGC/cGMP drug hunters; deep knowledge of nitric oxide (NO)-cGMP pathway

• broad experience in creating strong organizations and commercializing products
SCD and CNS:
creating breakthrough treatments
harnessing the power of soluble guanylate cyclase (sGC)