Human Genetics
A "human-first" drug discovery pipeline

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Forward-looking statements

This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to: our strategy and plans; potential of, and expectations for, our commercial business and pipeline programs; capital allocation and investment strategy; clinical development programs, clinical trials, and data readouts and presentations; risks and uncertainties associated with drug development and commercialization; regulatory discussions, submissions, filings, and approvals and the timing thereof; the potential benefits, safety, and efficacy of our and our collaboration partners’ products and investigational therapies; the anticipated benefits and potential of investments, collaborations, and business development activities; and our future financial and operating results. These forward-looking statements may be accompanied by such words as “aim,” “anticipate,” “believe,” “could,” “estimate,” “expect,” “forecast,” “goal,” “intend,” “may,” “plan,” “potential,” “possible,” “prospect,” “will,” “would,” and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

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These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements.
Drug targets with a genetic link to disease are more likely to succeed in the clinic and be approved

Genetic targets have at least double the probability of success

* >1/3 of FDA approvals in 2019 – 2020 are supported by genetics

Biogen’s disease areas have a substantial genetic component

- Single causative gene (SMA)
- Rare familial forms of more common disease (AD)
- Complex genetic disease – genetic risk may be estimated via measured polygenic risk score

Nelson et al, Nat Genet, 2015

AD = Alzheimer’s disease; ALS = amyotrophic lateral sclerosis; GWAS = genome wide association study; HD = Huntington’s disease; MS = multiple sclerosis; Ndev = neurodevelopmental; PD = Parkinson’s disease; SMA = spinal muscular atrophy
We have built a neuroscience translational platform that allows us to leverage advances in human genetics and inducible Pluripotent Stem Cell (iPSC) technologies.

Genetic Locus Discovery

Genes associated with disease onset, biology progression and protection
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- Genes associated with disease onset, biology progression and protection

**Causal Genes and Mechanism**
- Enrich for CNS data in human cohorts and Postmortem tissue
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**Functional Genomics**

Engineering patient mutations into disease relevant human functional assays or in vitro validation

FINN\textsuperscript{GEN} biobank

Pharma Proteomics Projects

THE SWEDISH BIOFINDER STUDY

MetaBrain

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**Observations in Humans**
- Prediction of clinical trial success
- Natural History in genetic subgroups
- Patient Stratification

**Causal Genes and Mechanism**
- Enrich for CNS data in human cohorts and Postmortem tissue

**Clinical Trials**

**Assays**

**Locus**

**Target**

**Functional Genomics**
- Engineering patient mutations into disease relevant human functional assays or in vitro validation

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Human genetics helps increase confidence at critical stages of pipeline

**Target Validation**

**Target ID:** Identify genes that impact disease biology & progression

**Drug Discovery**

**Patient stratification biomarkers:** Trial-ready genotyping assays & patient populations

**Drug Development Clinical Sciences**

**Genetic Testing Programs**

**De-risk target safety:** Identify safety risks that should be monitored

**Genetics of Randomized Clinical Trials:** Research on samples & data from our RCTs direct early-stage R&D efforts
Linking genetics to changes in Cerebral Spinal Fluid (CSF) protein levels to propose new CNS targets

CNS-focused molecular data

1. Acquire patient cerebrospinal fluid + plasma (N=1,600) from Swedish BioFINDER clinics

2. Measure relative concentrations of 400+ proteins

3. Perform genome-wide genotyping of protein concentrations

4. Conduct Mendelian randomization to infer causal associations (disease <- gene -> protein)

5. Identify novel AD, MS and neuropsychiatry targets with genetic validation*

Multiple sclerosis
9 potential drug targets

Alzheimer’s
9 potential drug targets

Depression
1 potential drug target

Bipolar & schizophrenia
2 potential drug targets

Whelan CD Acta Neuropathol Commun. 2019

AD = Alzheimer’s disease; CNS = central nervous system; MS = multiple sclerosis; p-tau = phosphorylated tau protein
Biogen acts as an architect to shape public resources to support drug discovery

**UK Biobank Exome Sequencing Consortium (UKB-ESC)**

**Biogen acts as an architect to shape public resources to support drug discovery**

**Linking UK Biobank exomes to phenotypes:** MAPT LoF is well-tolerated, increasing confidence in targeting tau

- 40 Predicted loss of function mutations
- 230 Heterozygous carriers
- No obvious safety concerns

Next step: Plasma tau to be measured in a subset of 53k samples to confirm finding

LoF = loss of function; MAPT = microtubule-associated protein tau

Carriers of 30-33 repeat alleles in ATXN2 show faster sALS progression, informing BIIB105 efficacy

Analysis of 1300 patients with genome wide data to identify genes

ATXN230-33 carriers have a 1.22/month faster rate of decline on the ALSFRS-R relative to ATXN220-23 carriers

McMillan et al American Academy Neurology Abstract 2020

ALSFRS-R = ALS functional rating scale-revised; ATXN2 = ataxin 2; sALS = sporadic ALS
Patient identification and confidence in pathogenicity is critical to progression of well-established genetic targets.

**Identify mutations**

- **EIMFS**: Epilepsy of infancy with Migrating Focal Seizures
- **EOEE**: Early-Onset Epilepsy Encephalopathy
- **SHE**: Sleep-related Hypermotor Epilepsy

290 Genes on Invitae Epilepsy Panel (including KCNT1)

**Do KCNT1 mutations show evidence of physiological gain-of-function in relevant cell types?**

- **Expression construct generation**
- **Xenopus oocyte expression**
  - Primary assay for rapid mutation classification
  - Well validated in academic literature

- **KCNT1 mutations**
  - GoF previously confirmed in vitro, in peer-reviewed studies
  - GoF reported but not confirmed
  - LoF reported in peer reviewed study
  - Common missense SNPs (no expected GoF)

**Engineered mutations in hiPSC derived neurons**

- Confirm in human neuronal system for key mutations

**CRISPR editing + neuron productions**

Identify patients for clinical trials

GoF = gain of function; hiPSC = human induced pluripotent stem cells
We work to be pioneers in translating human genetics to treat, prevent & cure diseases of the CNS

We have improved the quality & probability of success of our R&D pipeline, >75% of our pre-clinical portfolio is supported by human genetics