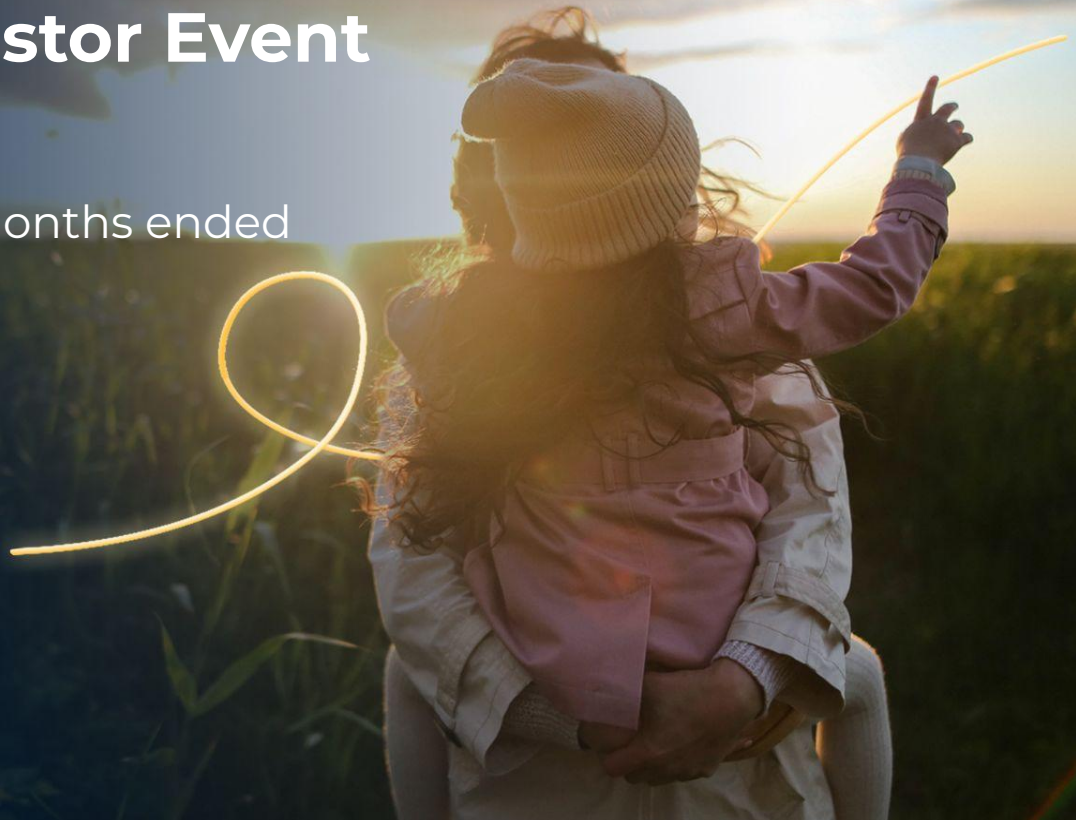
Analyst & Investor Event

AI in Drug Discovery &
Interim Results for 6 months ended
30 June 2022

27 September 2022



Benevolent AI

Disclaimer

Forward-Looking Statements

This document may contain forward-looking statements. Forward-looking statements are statements that are not historical facts and may be identified by words such as "plans", "targets", "aims", "believes", "expects", "anticipates", "intends", "estimates", "will", "may", "should" and similar expressions. Forward-looking statements include statements regarding objectives, goals, strategies, outlook and growth prospects; future plans, events or performance and potential for future growth; economic outlook and industry trends; developments in BenevolentAI's markets; the impact of regulatory initiatives; and/or the strength of BenevolentAI's competitors. These forward-looking statements reflect, at the time made, BenevolentAI's beliefs, intentions and current targets/aims. Forward-looking statements involve risks and uncertainties because they relate to events and depend on circumstances that may or may not occur in the future. The forward-looking statements in this release are based upon various assumptions based on, without limitation, management's examination of historical operating trends, data contained in BenevolentAI's records, and third-party data. Although BenevolentAI believes that these assumptions were reasonable when made, these assumptions are inherently subject to significant known and unknown risks, uncertainties, contingencies and other important factors which are difficult or impossible to predict and are beyond BenevolentAI's control.

Forward-looking statements are not guarantees of future performance and such risks, uncertainties, contingencies and other important factors could cause the actual outcomes and the results of operations, financial condition and liquidity of BenevolentAI or the industry to differ materially from those results expressed or implied by such forward-looking statements. The forward-looking statements speak only as of the date of this release. No representation or warranty is made that any of these forward-looking statements or forecasts will come to pass or that any forecast result will be achieved.

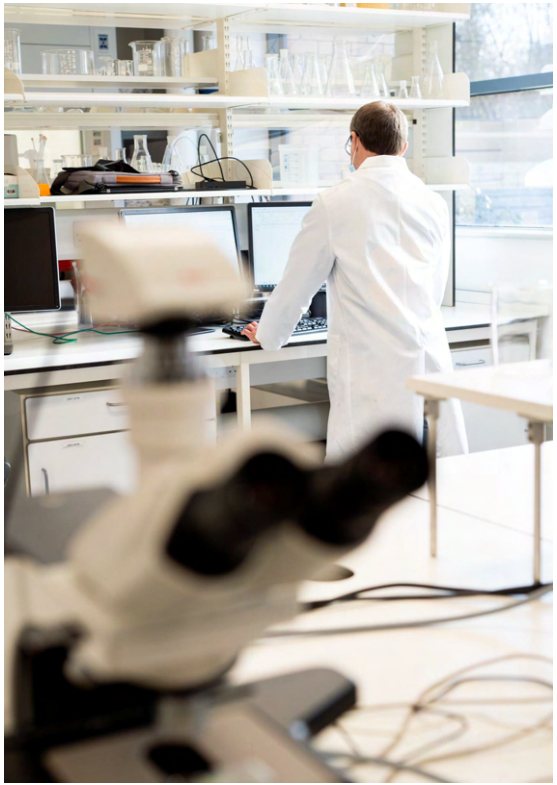
Opening Remarks & Introduction

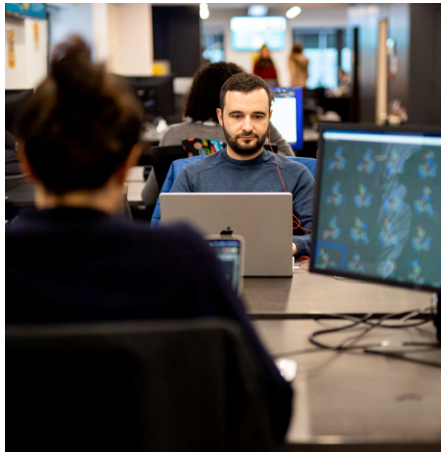
Joanna Shields, CEO

Benevolent AI

Benevolent AI

Because it matters





Clinical-stage AI-enabled drug discovery company

Uniting artificial intelligence with cutting-edge science to decipher complex disease biology and discover novel treatments

The Benevolent Platform™ is scientifically and commercially validated and has already delivered:

13 Named Platform-generated drug programmes

1 asset in Phase II

3 assets in pre-IND

+10 Exploratory stage programmes

Identified a leading **COVID-19 treatment** that is now **FDA approved**

Successful multi-target collaboration with AstraZeneca further validates our approach with a total of **3 novel targets** selected for AstraZeneca's portfolio

Well funded with key **value inflection points** in the **near and medium term**

Huge burden on society demands a new approach

96%
overall failure rate in drug development

$2.6bn
in average R&D and to market cost per drug

10 years
to market

30-50%
efficacy for leading drugs

Gaining a clear understanding of the **underlying molecular mechanisms of disease** based on the **totality of available biomedical data** is a vital step in the development of successful and efficacious treatments

Unprecedented opportunity to fundamentally rethink drug discovery

8.41
petabytes

of data managed by healthcare institutions in 2018, an increase of almost ninefold from 2016

4.5
petabytes

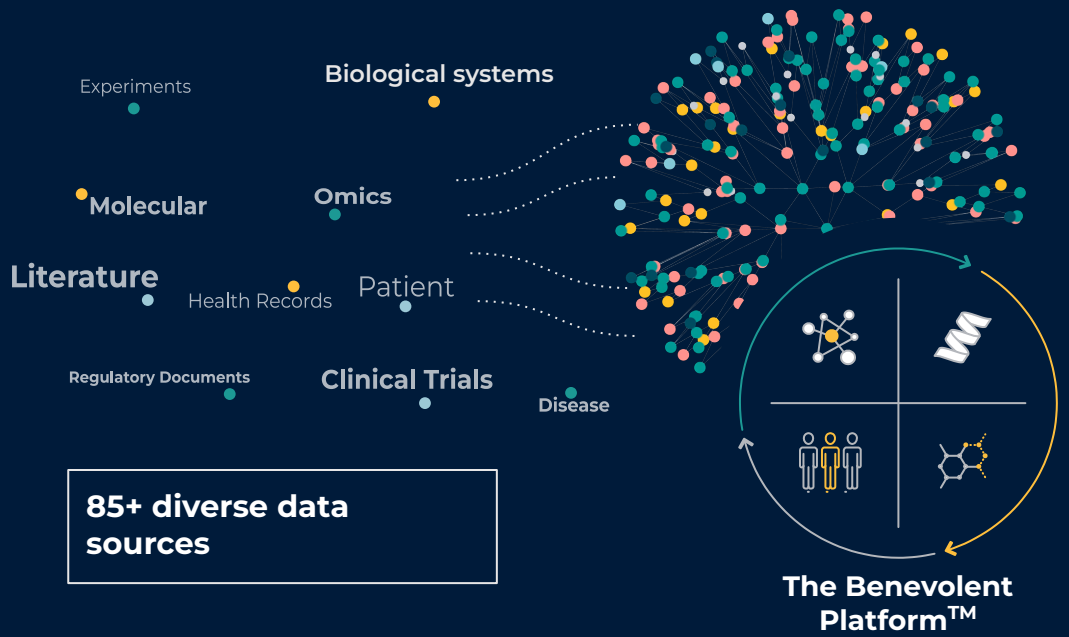
of data deposited to the **US National Cancer Institute's Genomic Data Commons** from 2016 to 2017

25
petabytes

of genomic data estimated to be produced annually worldwide by **2030**.

The **exponential growth** in the production and availability of **data**, combined with **advances in AI** and machine learning, create the unprecedented opportunity to **rethink the drug discovery and development process**

The Benevolent Platform™: a versatile, scalable and proven AI-enabled R&D engine



- Disease-agnostic
- Modality-agnostic
- Enables novel target ID
- Accelerates discovery
- Scalable and repeatable
- Potential to increase probability of success

About us

$300m in platform investment

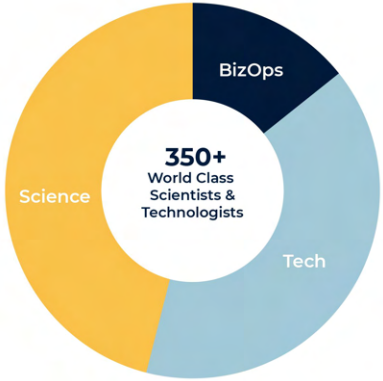
Board with deep expertise
across AI, drug discovery & development, pharmaceuticals

Listed on EuroNext Amsterdam
April 2022

Cash runway to Q4 2024
providing sufficient capital for key value inflection points

TEAM
as at June 2022

Full molecular biology, medicinal chemistry and *in vivo* pharmacology capabilities for in-house experimentation



BOARD


Baroness Joanna Shields
CEO & Executive Director


François Nader
Chairman


Susan Liautaud
Non-Executive Director


Olivier Brandicourt
Non-Executive Director


Jean Raby
Non-Executive Director


Jackie Hunter
Non-Executive Director


Nigel Shadbolt
Non-Executive Director


John Orloff
Non-Executive Director

Agenda

- **Market Context - AI-enabled drug discovery**
  Dr Ivan Griffin, COO
- **The BenevolentAI Business Model**
  Dr Ivan Griffin, COO
- **Our Approach and Technology**
  Dr Daniel Neil, CTO
  - *Dr Olly Oechsle, whiteboard animation of the Benevolent Platform™*
- **Drug Discovery and Pipeline Review**
  Dr Anne Phelan, CSO
  - *Professor Tom MacDonald - Immunology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London*
- **Interim Results 2022 - H1 Review & Financials**
  Nick Keher, CFO
- **Closing remarks & Outlook**
  Joanna Shields CEO
- **Q&A**

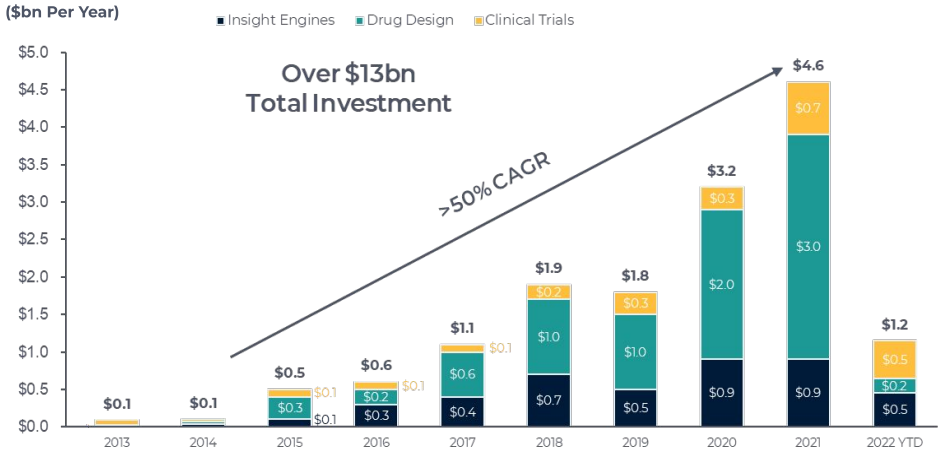
Market Context - AI-enabled drug discovery

Dr Ivan Griffin, COO and Co-Founder

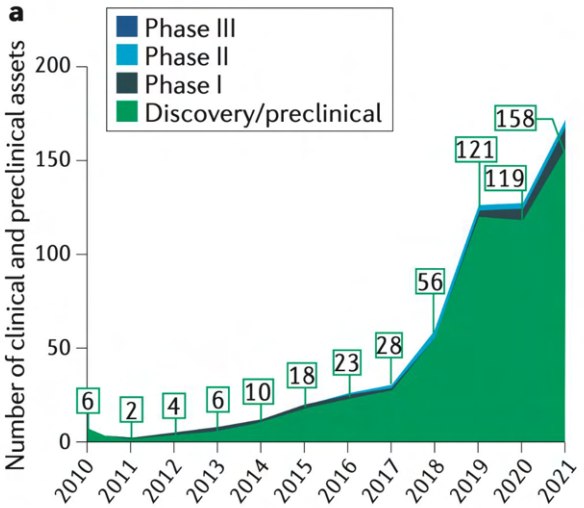
Benevolent AI

AI is becoming a validated approach in Pharma

Significant investment fuels massive growth for the AI market in drug discovery & development



AI-drug discovery companies' internal pipelines



This progress has been underpinned by three trends - advances in machine learning techniques, greater availability of biomedical data, increase in computational power

Source: RBC Capital Markets; Emersion Insights. Capital includes funds from private investors, VC and corporate investment funds. Company Websites and press releases. **Jayatunga et al. Nat Rev Drug Discov 2022:** Number of annual R&D programmes and assets over time, showing the growth of AI-enabled drug discovery. Note: Categories are mutually exclusive. Investment includes equity, Partnerships/collaborations and acquisitions

The AI value proposition for pharma R&D

Direct R&D Cost Savings

Discovery & Pre-Clinical

Increasing Probability of Success

Clinical Development

"Faster and cost effective"

INDUSTRY STANDARD	AI-ENHANCED
$33m over 5.5 years	$15m over 3-3.5 years

Based on industry benchmarks and internal programmes

Reduce pre-clinical cost by >50% and time to market by 2-2.5 years

Note
Lab research and target identification costs and time not captured in industry data - likely to add significantly to the industry standard time and cost

"Get it right more often"

Highest attrition is at Phase II (current 34% success rate)[2]

~50% Phase II/III trial failures due to **lack of efficacy**[3]

	INDUSTRY STANDARD	AI-ENHANCED (ILLUSTRATIVE)
PoS from Phase I to Market	12%	24%
# Phase I Candidates Required for 1 Approved Drug	9	4
Illustrative NPV[1]	c$60m	c$200m

Illustrative 25% PoS improvement at each clinical stage (Phase I-III)

Context

- Phase II trials with **pre-selection biomarkers** already **>50%** more likely to succeed[4]
- Industry experts estimate that the **use of AI** can improve the PoS of each phase by up to **45%**[5]

Notes and Sources: For illustrative purposes only; (1) Illustrative NPV for a theoretical $750m peak sales drug during initial 10Y on the market (assumes (i) peak sales reached 5 years post-launch, (ii) 90% gross margin, (iii) 20% S&M expenses, (iv) 20% tax, (v) a 10% discount rate) and (vi) excludes any terminal value). (2) Based on Paul et al Nat Rev Drug Discov 2010. (3) Based on Harrison, Nat Rev Drug Discov 2016. (4) Based on Biomedtracker/PharmaIntelligence 2021. (5) Based on Odyssey Due Diligence report.

Categorisation of AI/ML companies in biotech, hit & target-ID

Companies can be characterized across two key dimensions: **Original technology focus** and **drug discovery approach**

Target-ID

WHAT TARGET DO WE NEED TO HIT TO BE EFFECTIVE AND SAFE IN A SPECIFIC DISEASE (pathways, cellular processes)?

HIGH COMPLEXITY THROUGH BIOLOGY

Many layers of knowledge needed, and many areas where research is not yet complete

Hit-ID

HOW DO WE NEED TO HIT THE TARGET WE HAVE IDENTIFIED (specific drug characteristics)?

HIGH COMPUTATIONAL COMPLEXITY

Atom-to-atom interaction is relatively well known, but requires many calculations and simulations

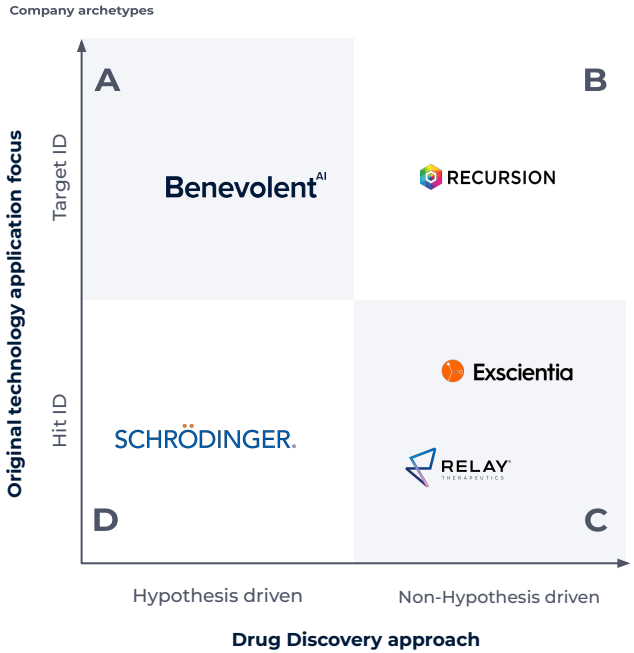


Figure: Oliver Wyman Analysis (listed companies only)

Source: Company Websites, Oliver Wyman Analysis

Hypothesis driven

Involves a **data-driven hypothesis-led** approach to therapeutic target identification

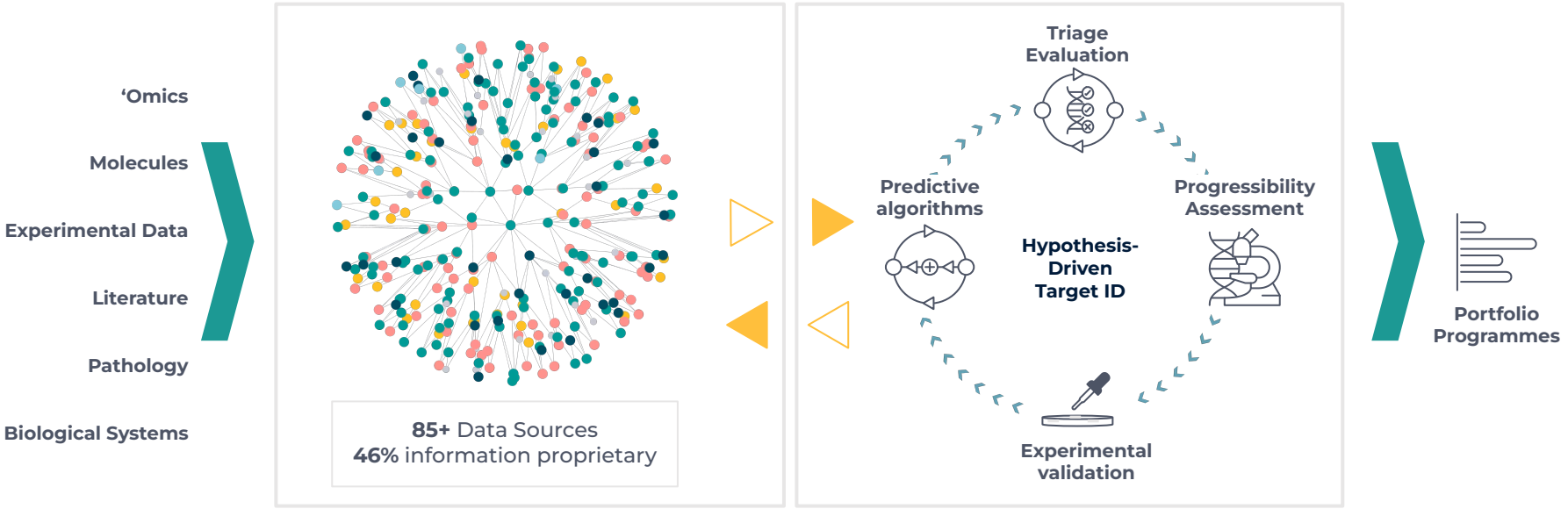
Non hypothesis driven

Leverages technology to identify solutions **without specific conditions to target specified at the outset**

Pharma companies also active in the space, through **internal development** and/or **collaborations**

BenevolentAI technology approach

Our data foundations integrate the world's relevant and available biomedical data to surface insights through our tools, improving how scientists discover and develop new therapies



1. Creating Data Foundations

Integrated knowledge platform built to ingest, represent, and surface insights from **large volumes of diverse data** types

2. AI Tools for Scientists

Suite of AI-driven tools and workflows allow scientists to explore data and discover **novel, high-quality targets**

Principles and benefits of our technology approach

Industry R&D CHALLENGES

- Half of **clinical failures** due to poor understanding of disease biology/mechanisms
- **Siloed disease-specific approach** – scientists can't connect or infer shared mechanisms across diseases
- **Single modality** data - each with **limitations** and **biases**
- Often **limited understanding** of what drives lab phenotypic effects
- Much of **target discovery** is **serendipitous**, not a scalable or repeatable process

BenevolentAI's APPROACH

1. **Biology first**
2. **Comprehensive data approach**
3. **Hypothesis driven**
4. **Software based**

Benevolent Platform™

BenevolentAI BENEFITS

- DISEASE-AGNOSTIC
- MODALITY-AGNOSTIC
- ENABLES NOVEL TARGET ID
- ACCELERATES DISCOVERY
- SCALABLE & REPEATABLE
- POTENTIAL TO INCREASE PROBABILITY OF SUCCESS

How BenevolentAI's approach compares to industry benchmarks

Deployment run for chosen disease

Typical proportion of targets identified validated by lab assay

23%

Potential increase in chance of a drug reaching the market vs industry benchmark

>2x (based on 25% increase in PoS at each clinical stage)

ACCURACY AND EFFICIENCY

Time from target to candidate

2 - 2.5 yrs

Potential time saved relative to industry benchmarks

At least **2 yrs**

TIME

Cost from target to IND

$15m

Potential cost benefit per IND relative to industry benchmarks

$18m saving **>50%**

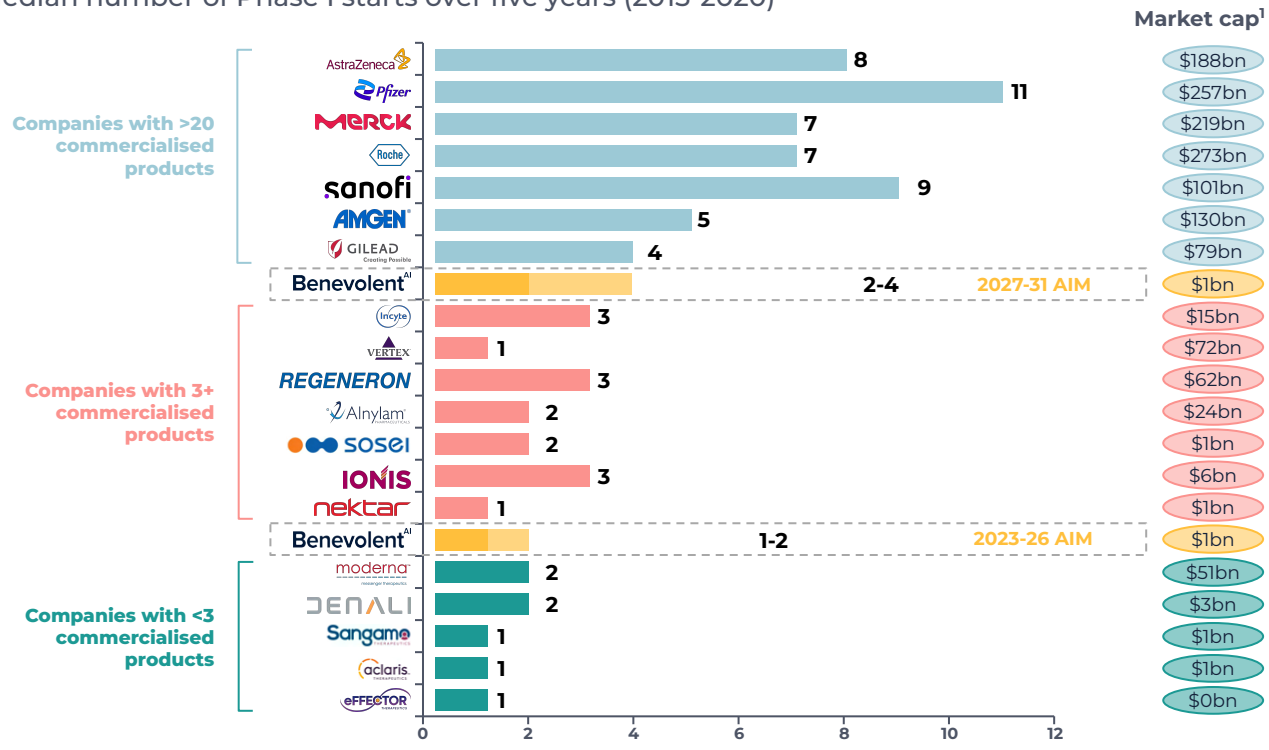
COST

Higher ROCE per $ spent on R&D

Industry benchmarks based on Paul et al Nat Rev Drug Discov 2010.

What that equates to: higher productivity

Number of new INDs filed by year by pharma and biotech companies
Median number of Phase I starts over five years (2015-2020)*



BenevolentAI potential **productivity** is in line with medium and large companies, but at a **fraction of the total cost**.

BenevolentAI will aim to increase the number of INDs from its Platform with incremental cost largely from development through to the clinic only

Note *IND filing rate is based on Phase I trial starts with the company as the lead sponsor. Average adjusted for companies which started clinical development during time period; [1] Market cap as of 06 September 2022

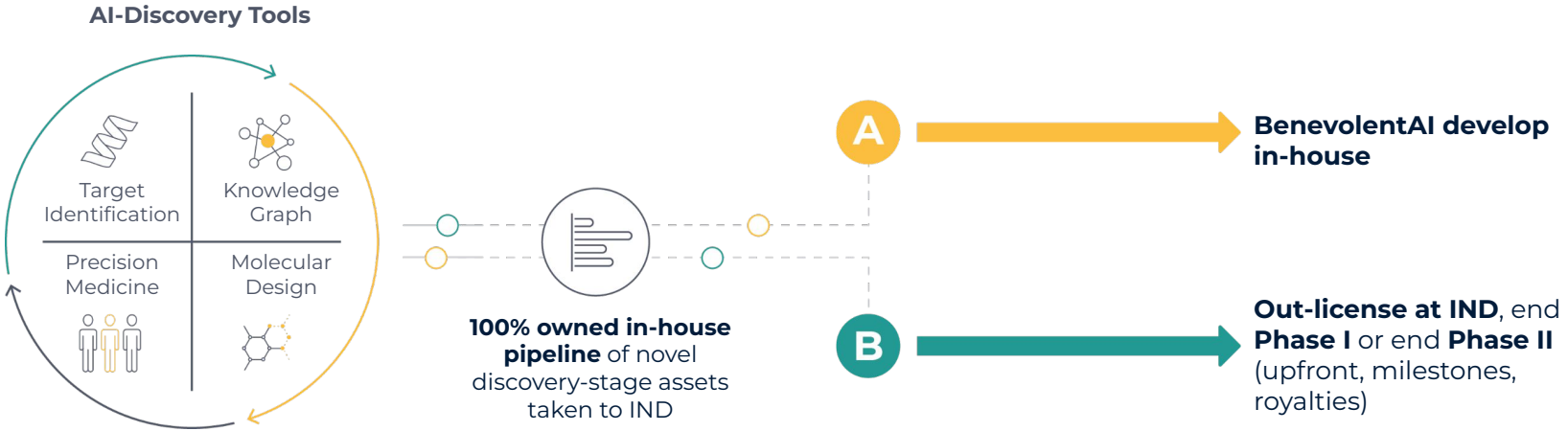
Source: clinicaltrials.gov ; Company websites: L.E.K. research & analysis

The BenevolentAI Business Model

Dr Ivan Griffin, COO and Co-Founder

Benevolent[AI]

The BenevolentAI business model — leveraging our technology platform to generate new drug IP at scale



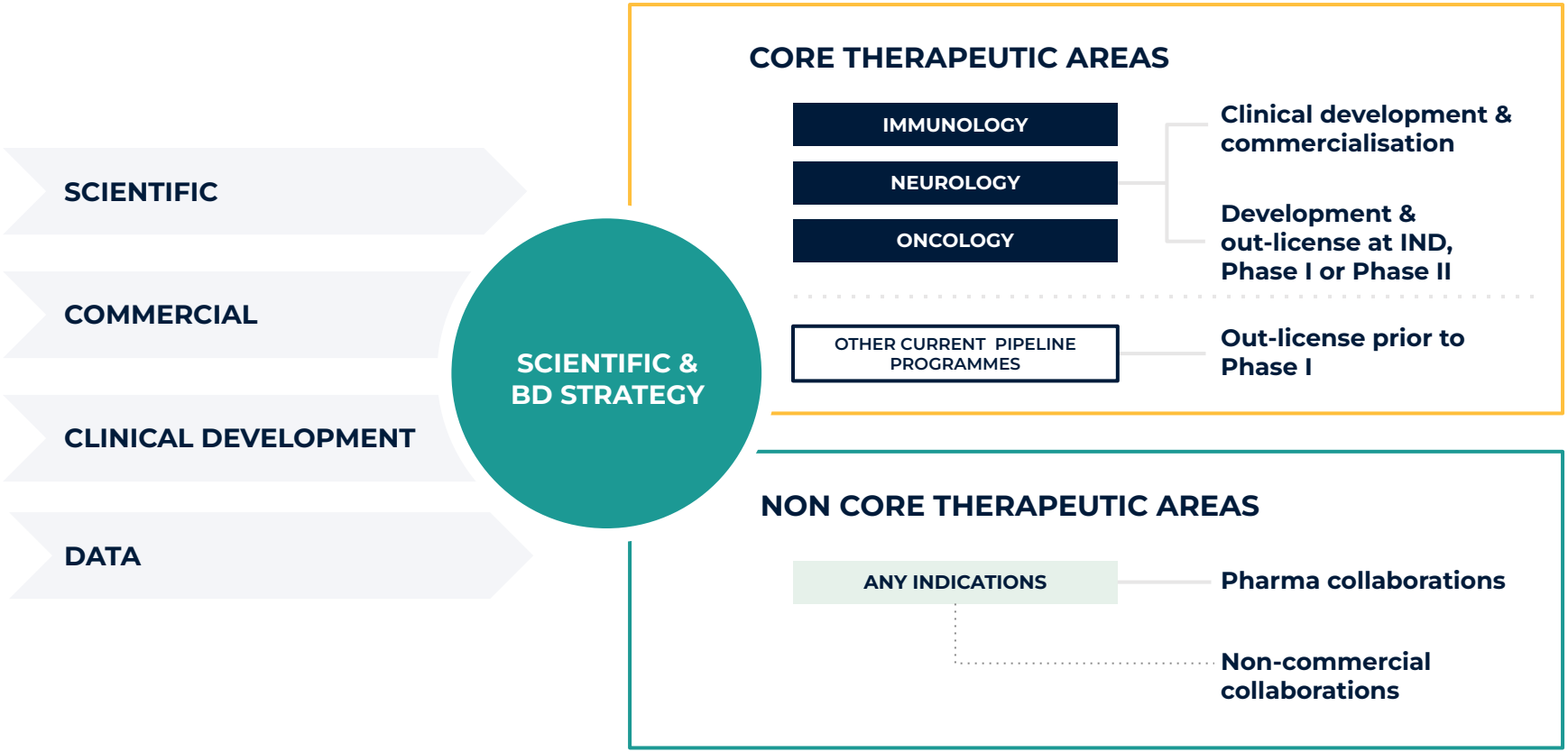
C **Pharma Collaborations:** Selective platform collaborations which can leverage the Platform in areas outside our core competencies

- Economic benefits
- Platform validation
- Data generated enriches the Benevolent Platform™

D **Non-commercial collaborations (DND*i*, COVID-19)**

- ESG
- Platform validation
- Data generated enriches the Benevolent Platform™

Therapy area and business model rationale

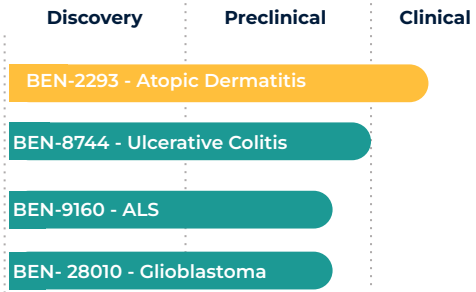


Benevolent Platform™: a validated approach

INTERNAL PIPELINE VALIDATION

Pipeline generated from the Benevolent Platform™

✔ One asset in **Phase II**, 3 assets in **pre-IND** and 13 **Named Platform-generated drug programmes**
+10 **Exploratory stage programmes**



✔**Disease-agnostic**

STRATEGIC VALIDATION

Successful delivery on multi-target long-term collaboration

AstraZeneca

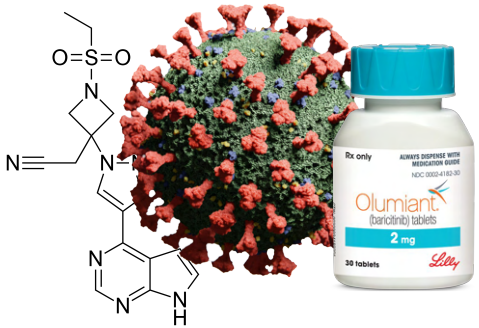
- **Chronic kidney disease (CKD)**
- **Idiopathic pulmonary fibrosis (IPF)**
- **Heart failure**
- **Systemic lupus erythematosus**

CLINICAL & REGULATORY VALIDATION

US FDA DRUG APPROVED

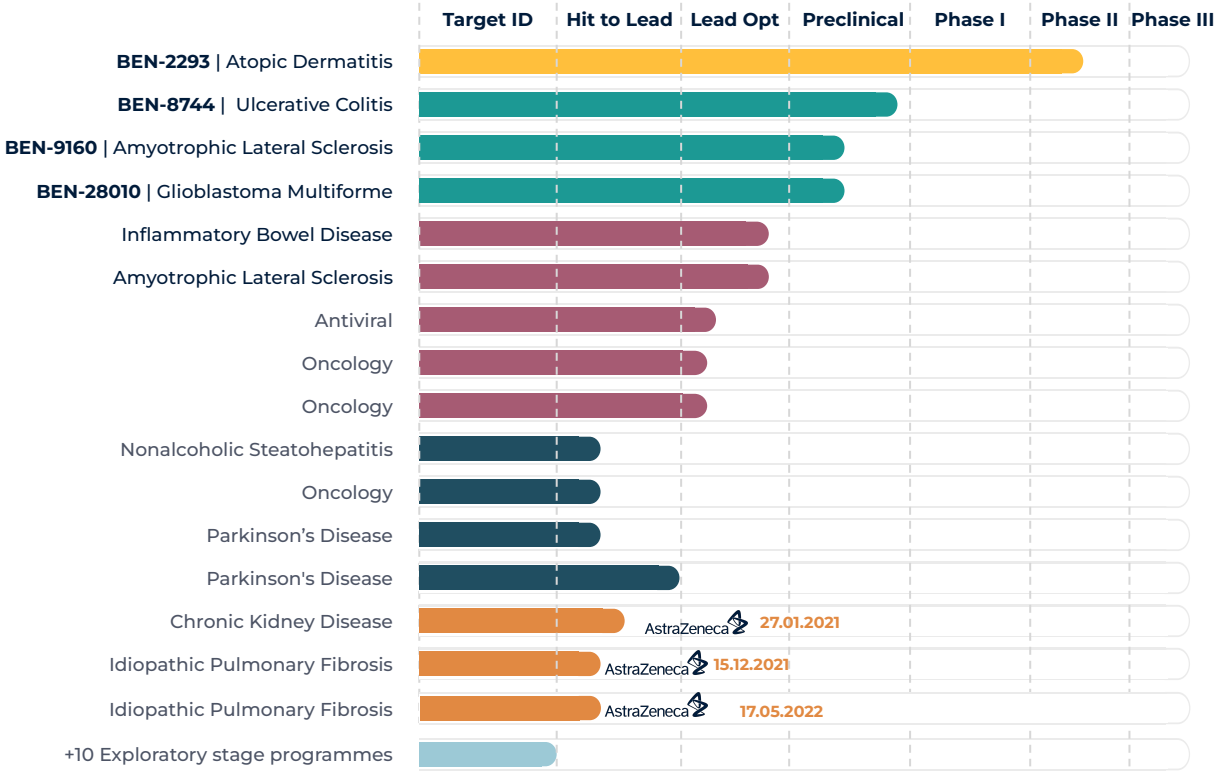
The Benevolent Platform™ successfully discovered an FDA approved treatment for COVID-19

Lilly



Olumiant Image source: olumiant.com/hcp/rheumatoid-arthritis/dosing

Internal validation: pipeline generated from the Benevolent Platform™



BEN-2293 -
Phase Ib complete, **Phase IIa ongoing**

BEN-8744
Novel target - zero prior linkage to UC

2 years from target validation to **candidate selection**

Broad disease coverage given platform

Balance of risk between "**best in class**" and "**first in class**" drug candidates

Strategic validation: successful collaboration with AstraZeneca

Multi-year Target-ID collaboration is delivering multiple, novel targets for complex diseases with high unmet need

- ✔ Separate data environment established to integrate AstraZeneca's data into a **bespoke Knowledge Graph**
- ✔ BenevolentAI and AstraZeneca teams working in **close collaboration** to explore, identify and validate targets
- ✔ Deal structure of **upfront license fee**, milestone payments and downstream royalties
- ✔ Collaboration enables BenevolentAI to enrich its platform via the data generated as part of the collaboration but also further validate the use of our AI platform

AstraZeneca

THERAPEUTIC AREAS

INITIAL DEAL (APRIL 2019)

Chronic kidney disease (CKD)

Idiopathic pulmonary fibrosis (IPF)

EXPANSION (DEC 2021)

Heart failure

Systemic lupus erythematosus

KEY MILESTONES

To date, **three novel targets** have been validated & **selected for AstraZeneca's portfolio**

- **CKD:** Jan 2021
- **IPF:** Dec 2021
- **IPF:** May 2022

Regulatory validation: identified a COVID-19 treatment now fully approved for use by the FDA

✔ **NOVEL**	Our technology and AI workflows identified a **previously unknown antiviral mechanism**[1]
✔ **RAPID**	The Benevolent Platform™ empowered scientists to rapidly formulate a **hypothesis in just 48 hours**
✔ **EFFECTIVE**	Baricitinib shown to reduce mortality from COVID-19 in randomised controlled trials: **COV-BARRIER trial showed baricitinib reduces mortality by 38%** in hospitalised patients[2], and by **46% in ventilated or ECMO patients**[3]
FDA U.S. FOOD & DRUG ADMINISTRATION	**FDA approved** the use of baricitinib to treat COVID-19 in **May 2022**[4] after first granting emergency use authorisation for baricitinib in combination with remdesivir in **Nov 2020**[5]

BenevolentAI published research in Feb 2020[1]

THE LANCET

Led to equity investment from Eli Lilly

Lilly

Sources: (1) Richardson et al. Lancet 2020; (2) Marconi et al. Lancet Respiratory Medicine 2021; (3) Ely et al. Lancet Respiratory Medicine 2022; (4) Lilly press release 11 May 2022; (5) Lilly press release 19 Nov 2020

Animated Benevolent Platform™ Video

Dr Olly Oechsle, Director of Engineering

Benevolent AI

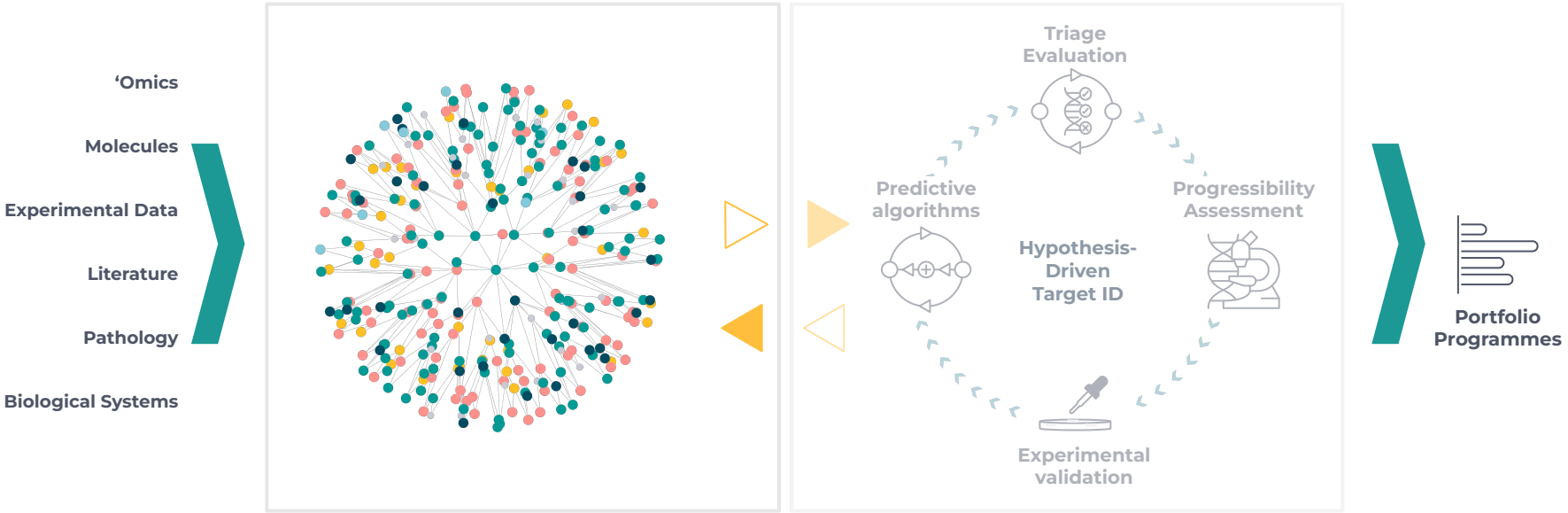
The BenevolentAI Approach & our Technology

Dr Daniel Neil, CTO

Benevolent[AI]

The Benevolent Platform™: Data Foundations and AI Tools

Our data foundations integrate the world's relevant and available biomedical data to surface insights through our tools, improving how scientists discover and develop new therapies



1. Data Foundations

Integrated knowledge platform built to ingest, represent, and surface insights from **large volumes of diverse data** types

2. AI Tools for Scientists

Suite of AI-driven tools and workflows allow scientists to explore data and discover **novel, high-quality targets**

Data Foundations integrate diverse data types

Experiments
Assay Data (Binding, Omics Comparison, CRISPR Screens)
Clinical Trial

OMICS
Genes
Proteins
Isoforms
Transcripts & Variants

Molecules
Organic Compounds
Preclinical Candidates
Approved Drugs
Antibodies
Other Biologics
Pharmacology
Pharmacokinetics

Literature
Scientific Literature
Patent Literature
Regulatory Documents

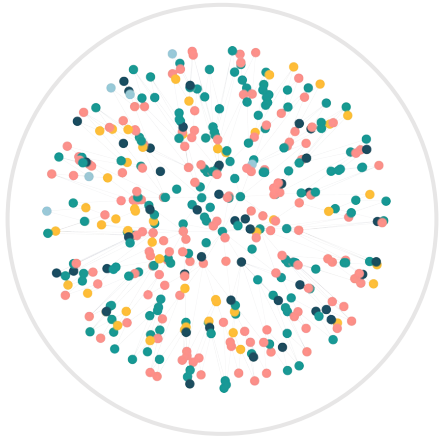
Aetiology
Diseases
Symptoms

Biological Systems
Cellular Component
Molecular Function
Biological Process
Mechanism
Pathways

DATA PROCESSING PIPELINES

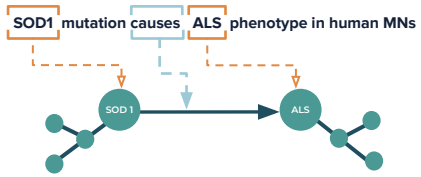
CLINICAL DATA
TRANSCRIPTOMICS
CLINICAL DATABASES
LITERATURE

EXTRACTED & INFERRED DATA



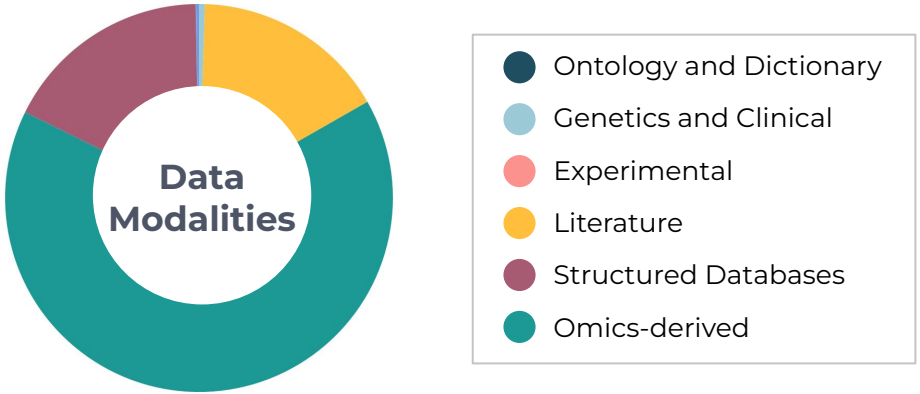
THE DATA FOUNDATION OF OUR PLATFORM

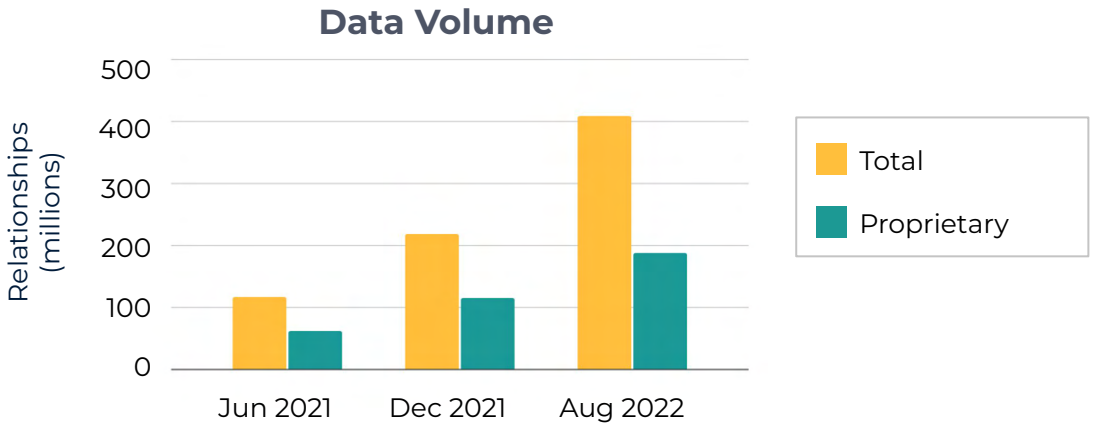
Natural Language Processing:
Named Entity Recognition & Relationship extraction



✔ Integrates **85+ disparate data sources**
✔ A data foundation that is **proprietary, and scalable**

The BenevolentAI Data Foundations, in numbers





85+

Data sources

409m

Biomedical relationships

33

Entity types

46%

Proprietary information

Data modalities paired with processing pipelines

Literature processing pipeline

DBs

APIs

Files

Automated Download and Ingestion

Reliably bring in fresh, up-to-date scientific literature

Document Normaliser

Standardize and remap the text for further processing

Named Entity Recognition

Identify the key concepts in the text

Relation Extraction Methods

Rule-based Methods

ML-based Methods

Extract relationships between identified biomedical concepts

Identifier Builder

Ensure consistent entities across the platform

Precision Medicine genetics processing pipeline

Genetic Summary Stats

Genetic Cohorts

Annotation Features
(eQTL/pQTL, chromatin, locus features, etc.)

GWAS Pipeline

Spark-enabled, scalable pipeline to link traits to variants

WES / WGS Pipeline

Spark-enabled, scalable pipeline to link traits to variants

Variant-to-Gene Annotation

Match variants to an associated gene

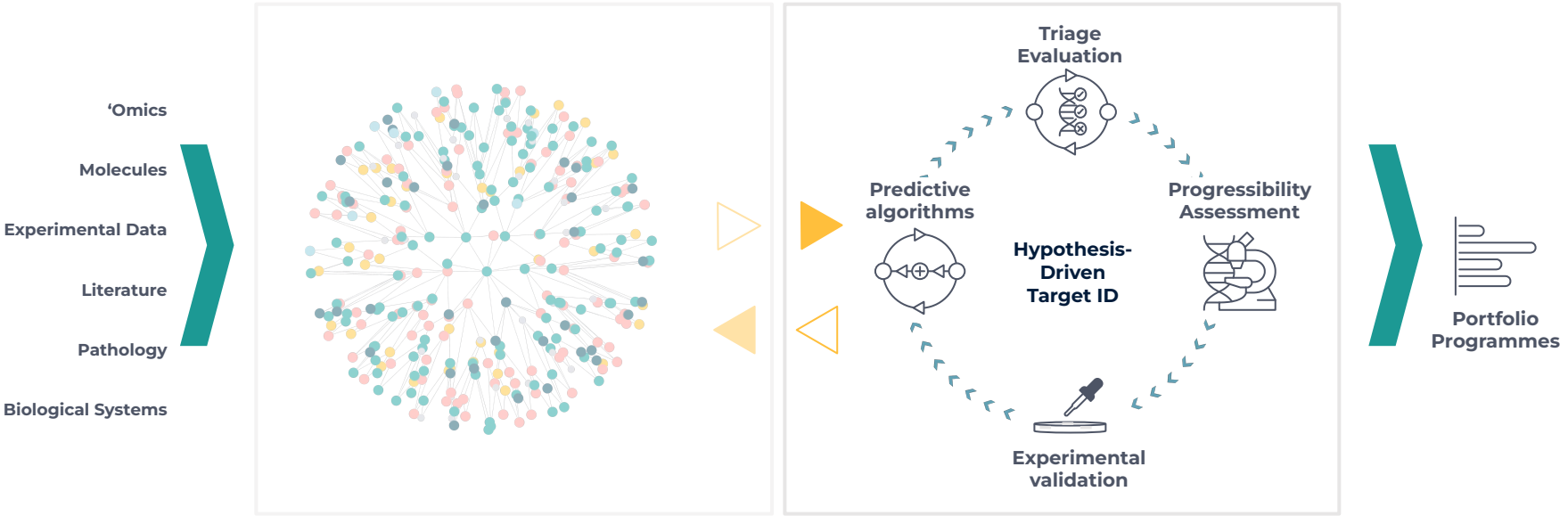
Representation Harmonisation

Ensure consistent genetic linkage

EXTRACTED & INFERRED DATA

The Benevolent Platform™: Data Foundations and AI Tools

Our data foundations integrate the world's relevant and available biomedical data to surface insights through our tools, improving how scientists discover and develop new therapies



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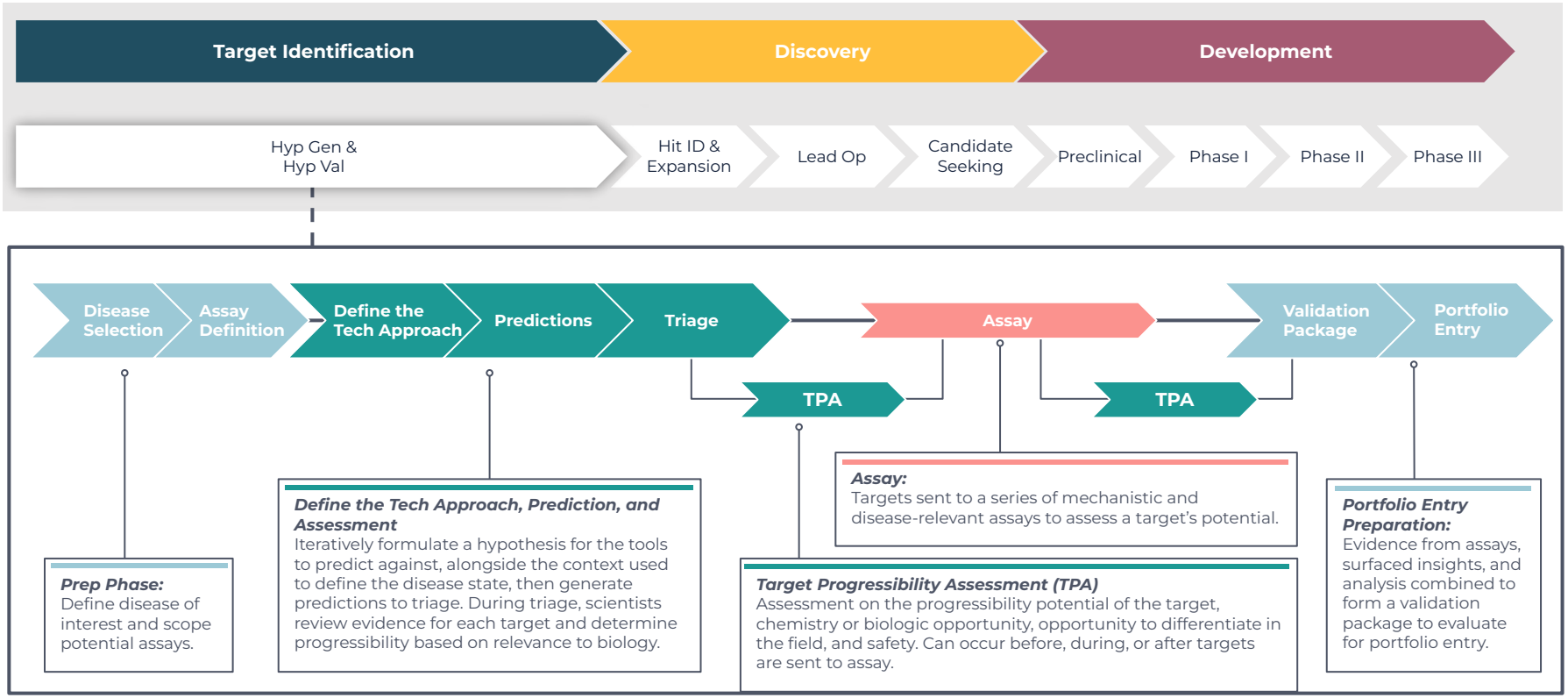
BenevolentAI's Target ID workflow and tools



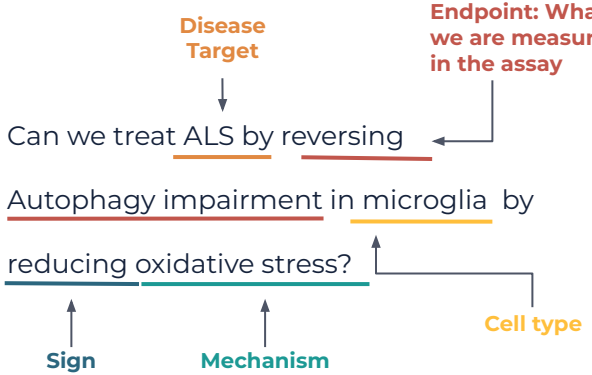
BenevolentAI TID Tool Portfolio

BenevolentAI's target discovery tools and process identifies promising, novel therapeutic targets

TECH APPROACH
PREDICT
TRIAGE
TPA
ASSAY

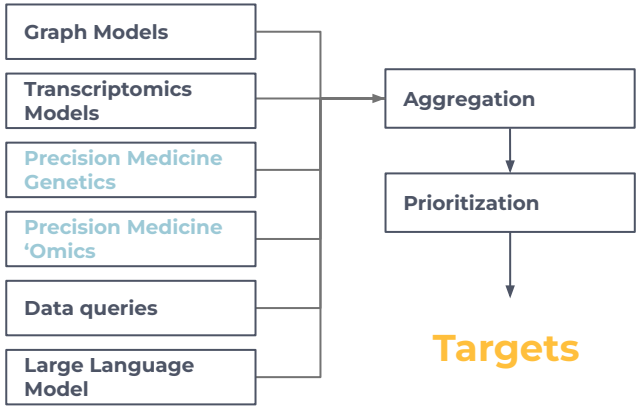
1. Define the Tech Approach

Using our in-house tools and algorithms we explore the data and **define the input to our predictive models**



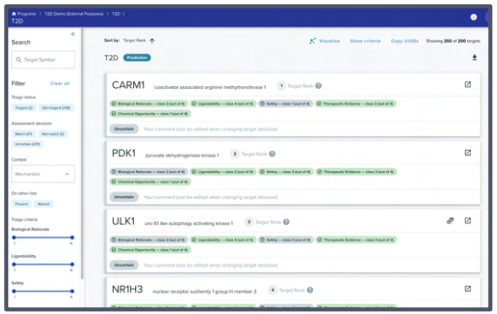
2. Target Prediction

Our AI algorithms, data queries, and endotype-driven workflows **identify targets** that are likely to address the tech approach.



3. Triage and Assess Progressibility

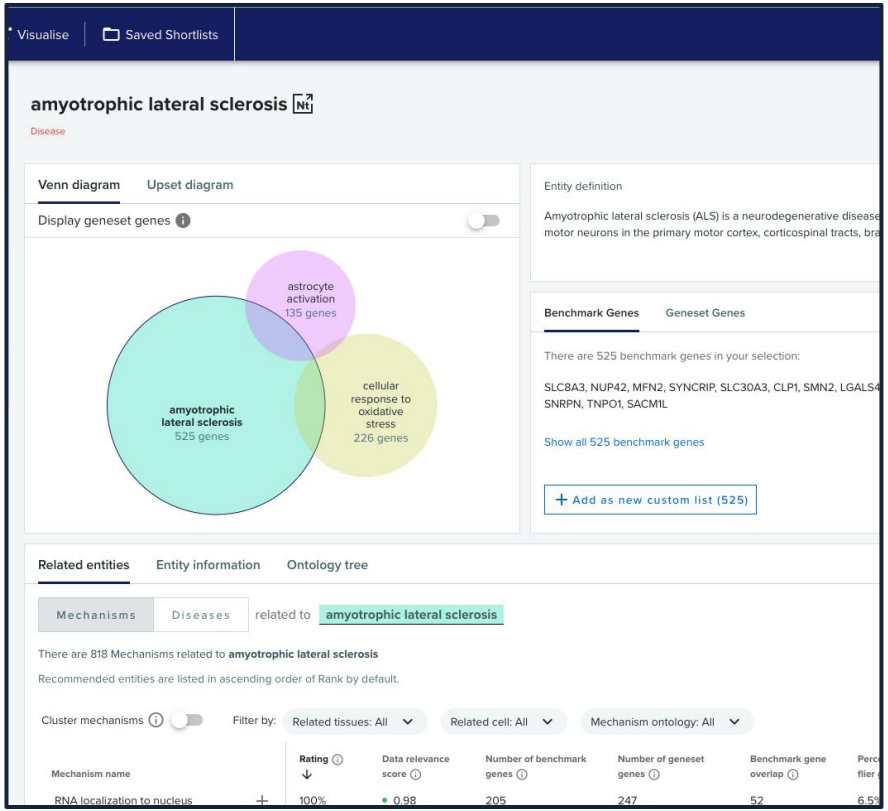
Our tools aggregate and present the necessary data for scientific decision-making, progressing only the most promising hypotheses.

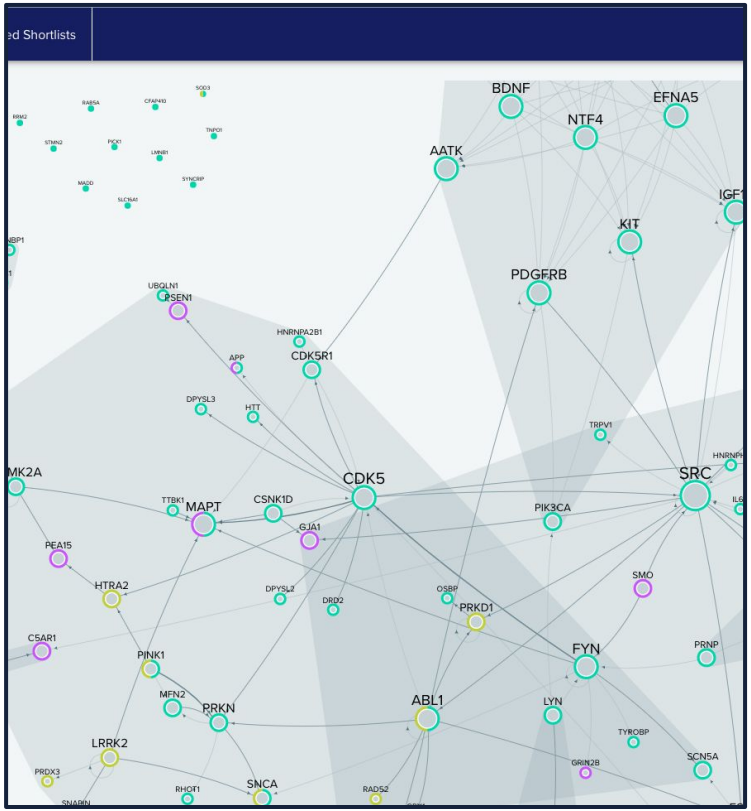


4. Validate Experimentally

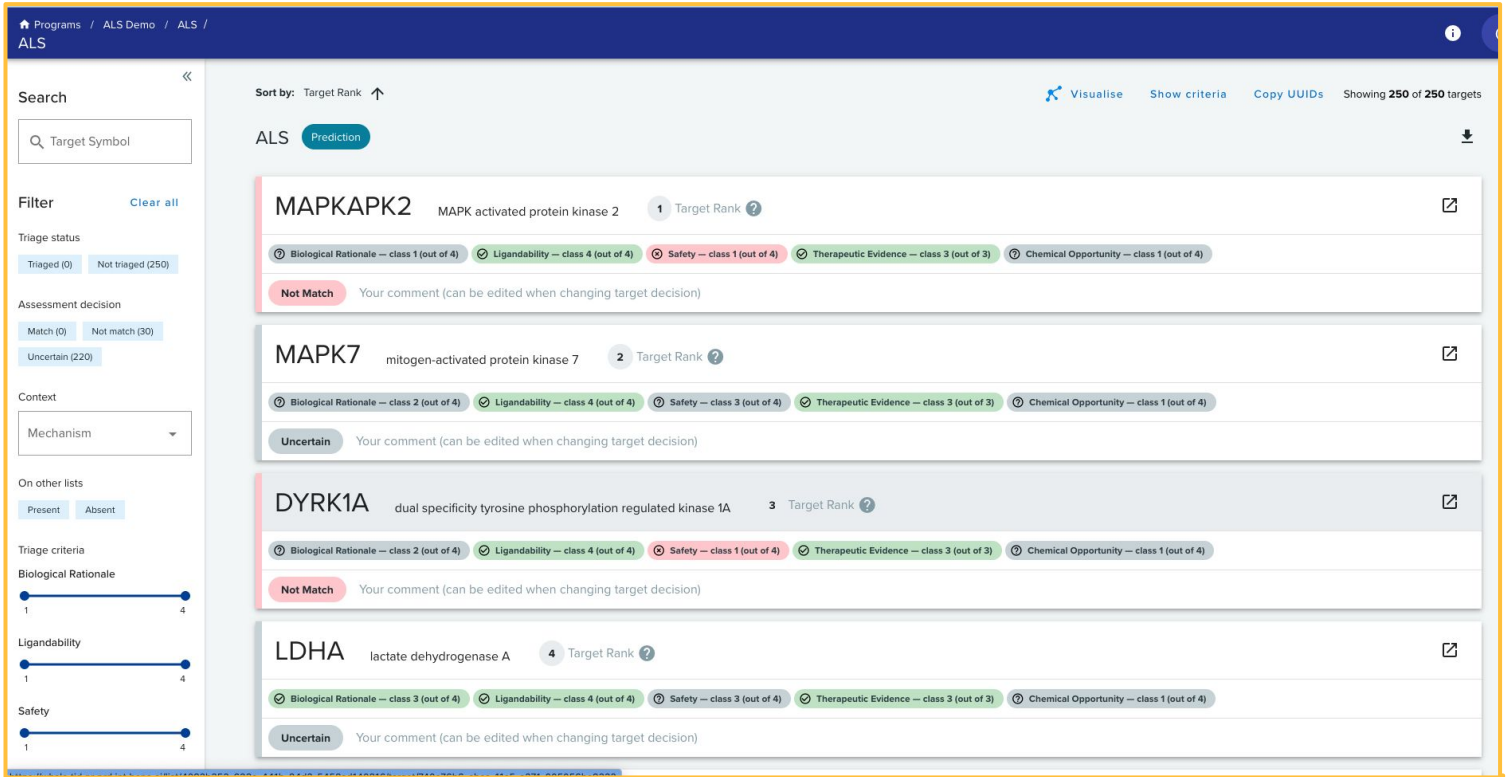
Targets sent to a series of mechanistic and disease-relevant assays to assess a target's potential.

Define the tech approach by exploring the data



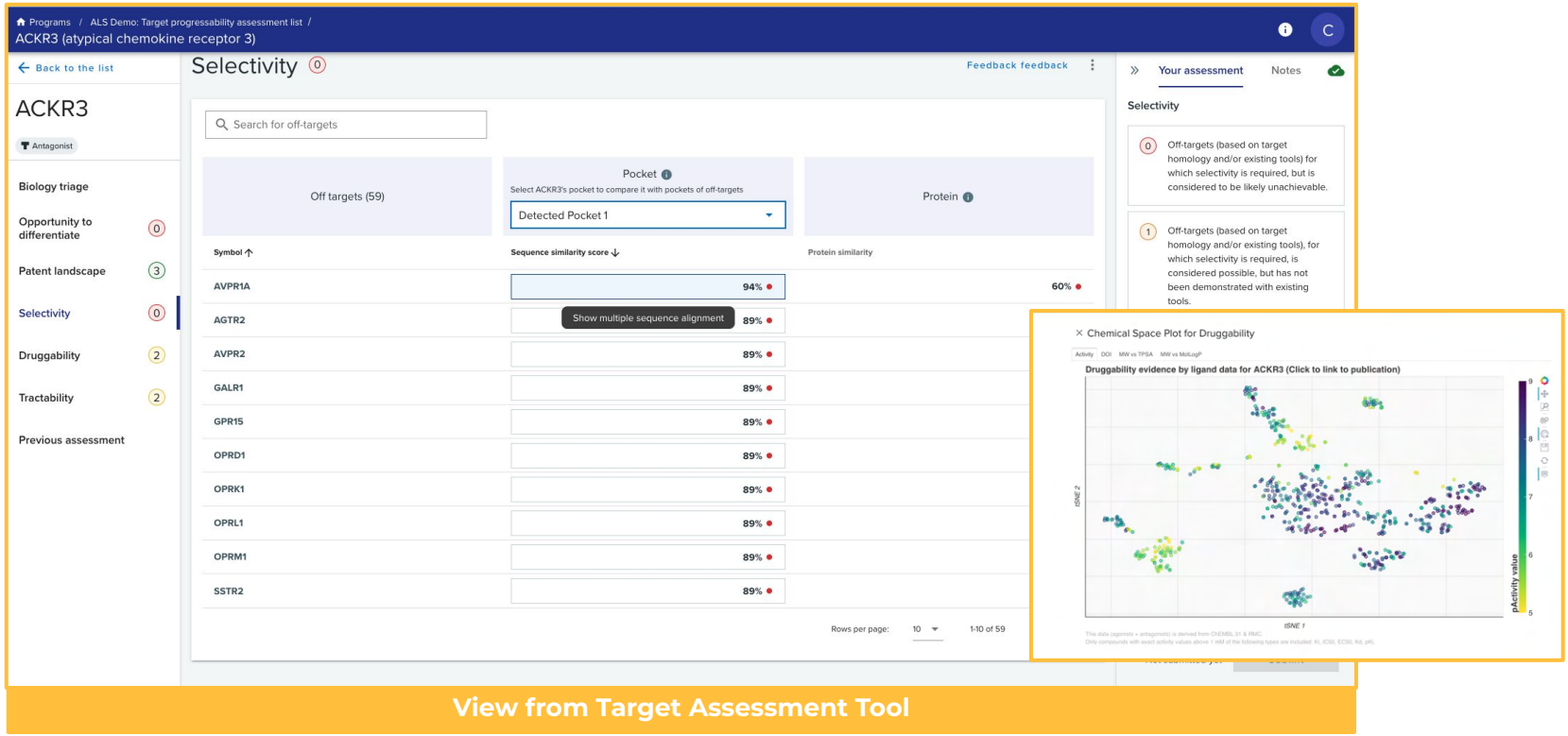


Triage targets to select only the most promising hypotheses



View from the Triage Tool

Target Progressibility Assessment (TPA): Identify the hypotheses most likely to succeed



View from Target Assessment Tool

Benefits from our technology approach

DISEASE-AGNOSTIC

Enabled by: a focus on breadth of biomedical information and the integration of diverse, wide-ranging data types.

MODALITY-AGNOSTIC

Enabled by: early Target ID tools supporting both small molecule and biologics approaches.

NOVEL TARGET

Enabled by: large volumes of integrated data can surface novel targets never considered before - and spark creativity in scientists.

ACCELERATES DISCOVERY

Enabled by: supporting scientists with aggregated, summarised information and tools to support efficient decisions

SCALABLE & REPEATABLE

Enabled by: workflows and software foundations designed for scale, run repeatedly for internal deployment and external collaborators.

POTENTIAL TO INCREASE PROBABILITY OF SUCCESS

Enabled by: tools enabling early data-driven decisions to progress only the most promising hypotheses.

Drug Discovery & Pipeline Review

Dr Anne Phelan, CSO

Benevolent AI

Advanced laboratory capabilities help move programmes faster, and generate data at scale for continuous innovation

Advanced capabilities and technologies

- **Fully equipped laboratory** facilities; Biology, Chemistry, CMC, DMPK.
- **Highly experienced scientists** across all drug discovery disciplines
- In-house investment in **CRISPR**, **RNA seq** and **human iPSC** capabilities
- Robust and secure data storage capacity
- Access to the **Babraham Institute Research facility**, with state of the art High Content Imaging and FACs capabilities.
- **CROs** and **academic** collaborations complement and extend internal capabilities

Experimental capabilities enhance entire drug discovery process

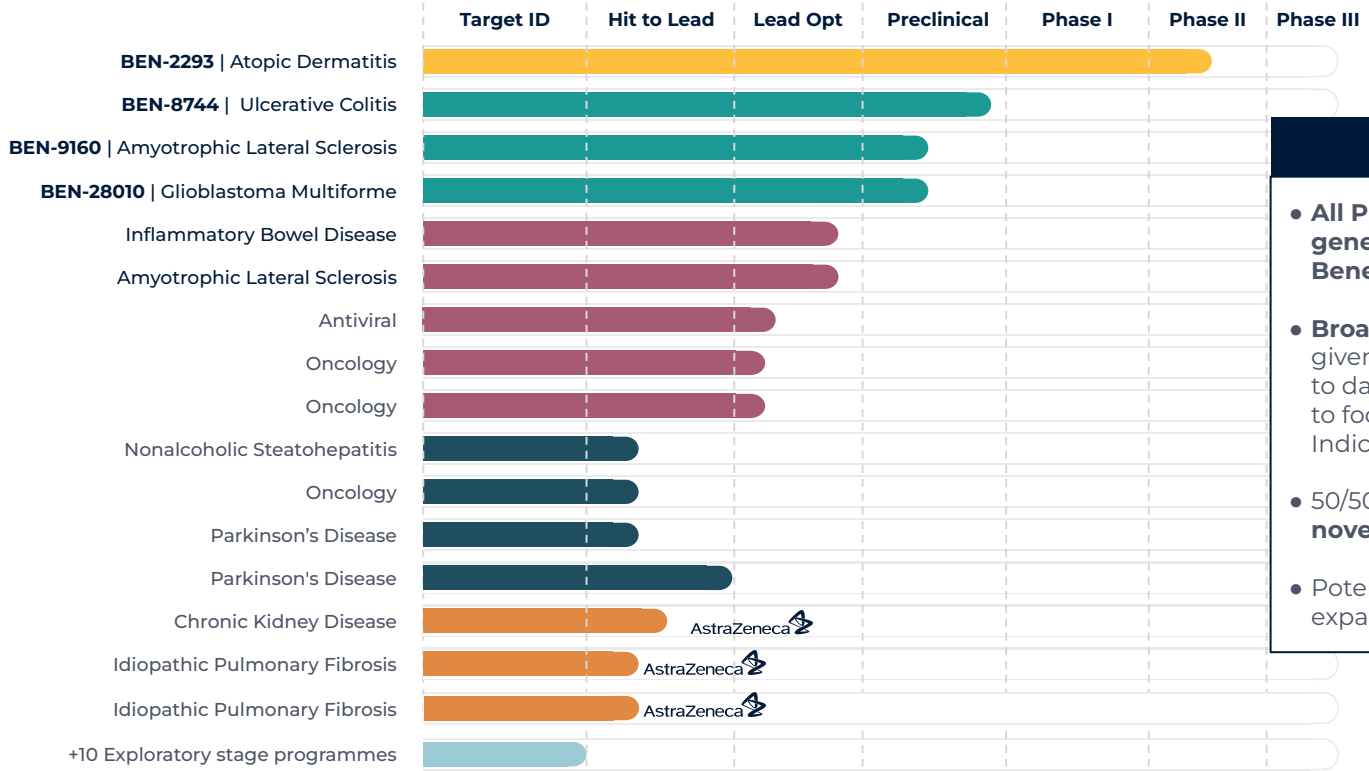
- Mechanism selection, **Target identification,** target triage and experimental validation
- Refined, model-enabled **Design-Make-Test cycle**

Closing the data loop

- Experimental data from hypothesis validation workflows, portfolio projects and disease relevant **expression data** are integrated back to further **enrich the knowledge graph and our representation of human biology**

Work progresses rapidly from in-silico to in-vitro experimental test
Dynamic experimental feedback loop between scientists & technologists

Internal validation: pipeline generated from the Benevolent Platform™

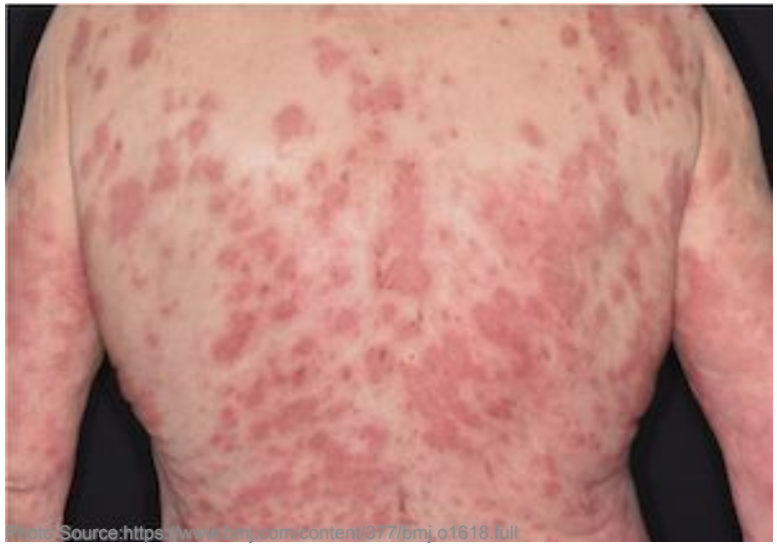


Highlights

- **All Pipeline programmes generated from the Benevolent Platform™**
- **Broad therapy area coverage** given disease-agnostic approach to date, with future investment to focus on three Therapeutic Indications
- 50/50 mix of **Best in class** and **novel / First in Class indications**
- Potential for **rapid scaling** and expansion into **new modalities**

BEN-2293 - Atopic Dermatitis (AD)

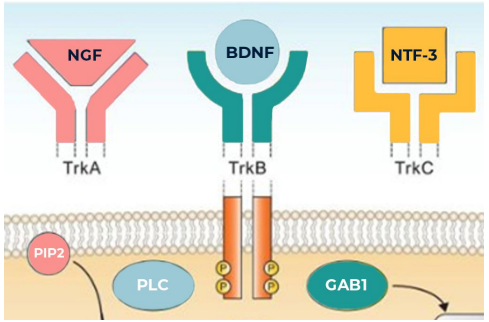
- Atopic dermatitis is the most common chronic inflammatory skin disease, characterized by intensely itchy, red, and swollen skin[1]
  - Affects **10-20% of children** and up to **3% of adults**[2]
  - Approximately **60-70% of all cases** present with mild-moderate disease severity[3]
  - Prevalence is rising[3], with market value in 7MM **forecast to exceed $14 billion**[2,4]
- Skin inflammation and chronic pruritus associated with atopic dermatitis negatively impact quality of life and psychosocial well-being[1]
- Clear unmet need in **mild to moderate patient** segment for treatment addressing itch and inflammation, without side effects of steroids



Sources: (1) Weidinger et al. Nat Rev Dis Primers 2018; (2) GlobalData Report 2018: Atopic Dermatitis: Global Drug Forecast and Market Analysis to 2027; (3) GlobalData Report 2018: Atopic Dermatitis: Epidemiology Forecast to 2027; (4) Evaluate Pharma

BEN-2293 - A potent PanTrk antagonist developed to relieve inflammation and provide rapid itch resolution Atopic Dermatitis

- **BEN-2293** is a **PanTrk inhibitor** targeting TrkA, B and C receptors. The Trk receptors were identified as part of an effort to find **mediators of both itch and inflammation in AD**. Using our Molecular Design expertise we were able to design a PanTrk inhibitor, equipotent against the 3 receptors
- BEN-2293 is expected to **treat atopic dermatitis** by: inhibiting **itch signaling** and blocking nerve sensitization (TrkA) in addition to inhibiting Th1 and Th2-mediated **dermal inflammation** (TrkB, TrkC)
- **BEN-2293** will target **Mild, Moderate and Severe Atopic Dermatitis patients**, addressing unmet need in the treatment of mild to moderate Atopic Dermatitis as a steroid sparing alternative and in more severe patients undergoing treatment with biologics (e.g. dupilumab) that require add-on treatment



Neurotrophins bind to high affinity receptors (TrkA, B and C), directly activating both inflammation and itch signalling which propagates a cycle of itching and scratching.

Key: Tropomyosin-related kinase (Trk) receptor tyrosine kinase family, namely TrkA, TrkB, and TrkC; Nerve Growth Factor (NGF); Brain Derived Neurotrophic Factor (BDNF); Neurotrophin-3 (NTF-3)/NT3
Image source: Amatu et al. ESMO Open 2016

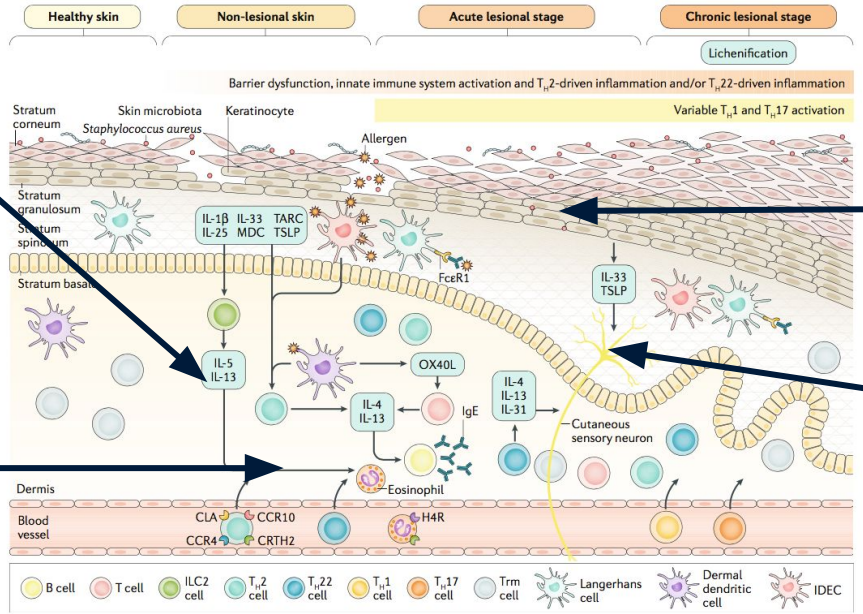
Atopic Dermatitis – BEN-2293, PanTrk rationale

TrkC

- NT3/TrkC potentiates stimulated ***Th2 T-cell*** inflammatory responses and synergistically enhances T-cell receptor induced IL-4 production by Th2 cells
- ***Mast cells*** within AD skin lesions express high levels of NT3 compared to normal controls

TrkB

- AD skin-resident ***eosinophils*** express elevated levels of TrkB (together with TrkA and C) and functionally respond to BDNF
- BDNF/TrkB inhibit eosinophil apoptosis and increase chemotactic index



TrkA

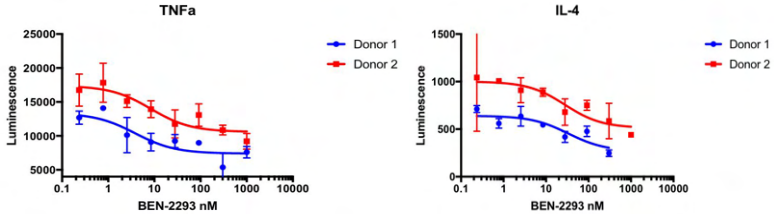
- TrkA levels in skin dramatically increase in response to inflammatory stimuli
- NGF produced by AD ***keratinocytes*** is a major mediator of cutaneous hyperinnervation
- Increased NGF in the skin sensitizes ***primary afferents*** contributing to peripheral itch sensitization and chronic pruritus
- Involved in the inflammatory activation of ***mast cells*** and ***basophils***

Source: Weidinger et al. Nat Rev Dis Primers 2018

We expect BEN-2293 to provide both symptomatic relief and to reverse disease progression in atopic dermatitis

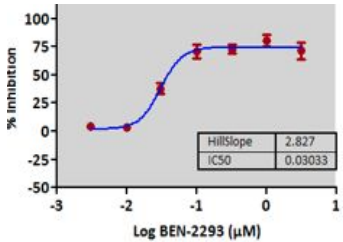
- **BEN-2293 is highly selective for Trk receptors,** with IC50 potencies in the low nM range for TrkA, B, and C
- **BEN-2293 dose dependently inhibits release of inflammatory Th1 and Th2 cytokines** TNFα, IFNɣ, IL-13, and IL-4 in human peripheral blood mononuclear cells (PBMCs) stimulated with an inflammatory T-cell stimulus (anti-CD3/CD28)
- **BEN-2293 inhibits the release of Calcitonin Gene-Related Peptide (CGRP)**, a mediator of itch, sensory nerve hypersensitisation and neurogenic inflammation, in dorsal root ganglion (DRG) isolated from adult rats and stimulated with NGF
- **BEN-2293 series significantly (p<0.05) reduced mouse ear inflammation** following administration of PMA, significantly reducing expression of cytokines IL-1β, IL-4, IL-6, CXCL1, MCP-1, and Tarc
- **BEN-2293 demonstrates excellent tolerability and safety margins** in IND/CTA-enabling toxicology studies

BEN-2293 Inhibition of human primary T-cell activation

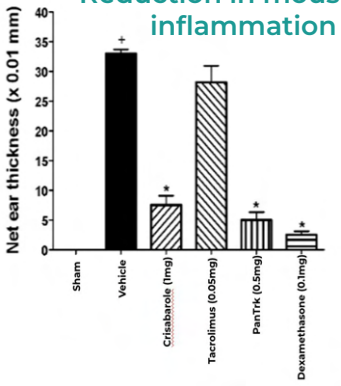


Human PBMCs from 2 donors. Anti-CD3/CD28 stimulus +/- BEN-2293

Inhibition of sensory neuron activation



Reduction in mouse ear inflammation



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BEN-2293 - Phase Ib safety and tolerability study successfully completed

Phase Ib/IIa double-blind, placebo-controlled, first-in-patient, two-part clinical study

Phase Ib

1 → 2 → 3 → 4

First-in-human dose escalation

Phase Ib completed Dec 2021

8 Mild-Moderate AD patients (18-65 years) per cohort, randomised 3:1 BEN-2293:Placebo

Safety, Tolerability, PK

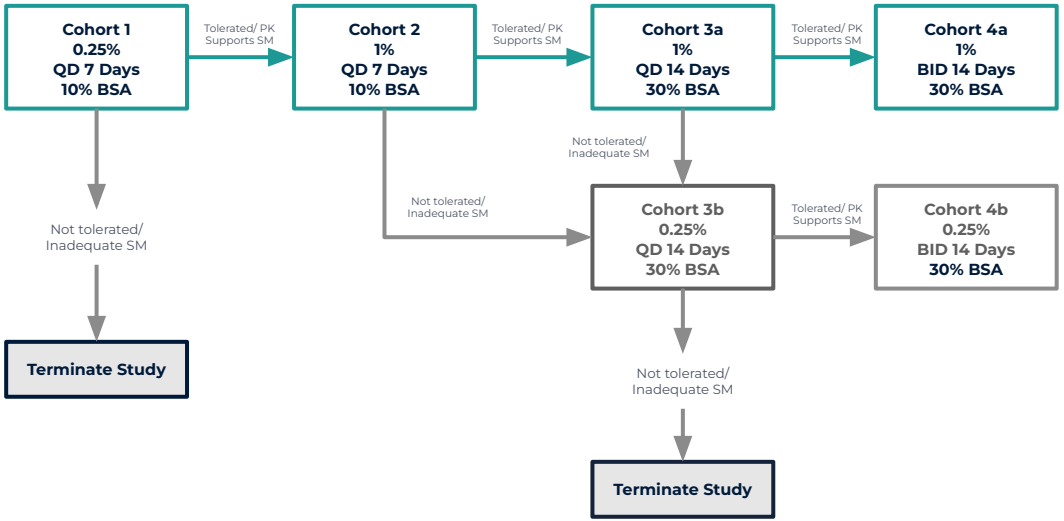
- Adaptive multiple ascending dose cohort design
- Includes efficacy endpoints
- MALDI imaging
  - To evaluate human skin PK

Phase Ib:

✔ **Successfully completed**

Safety and Tolerability arm

Adaptive design for Phase Ib of the clinical study



BSA= Body surface area. QD = once per day dosing BID= twice per day dosing

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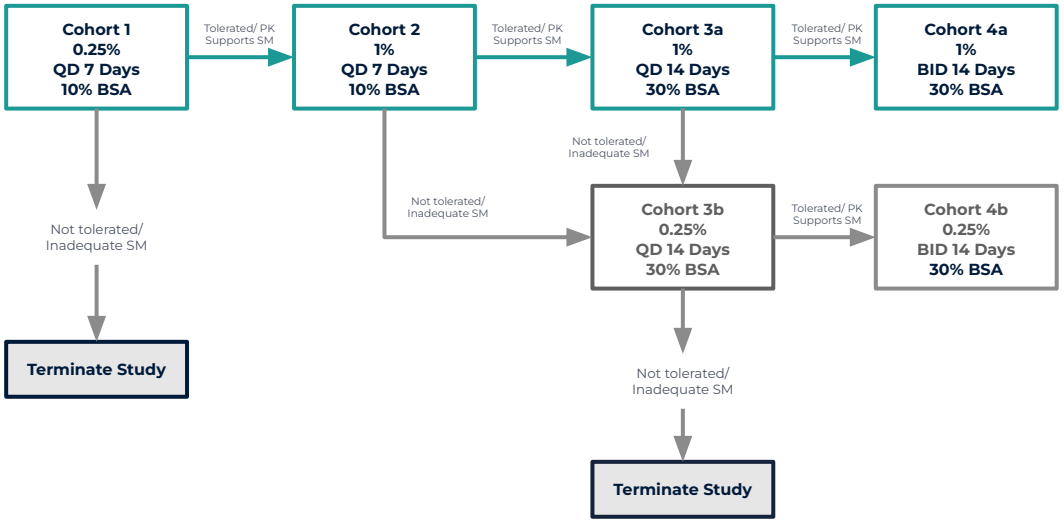


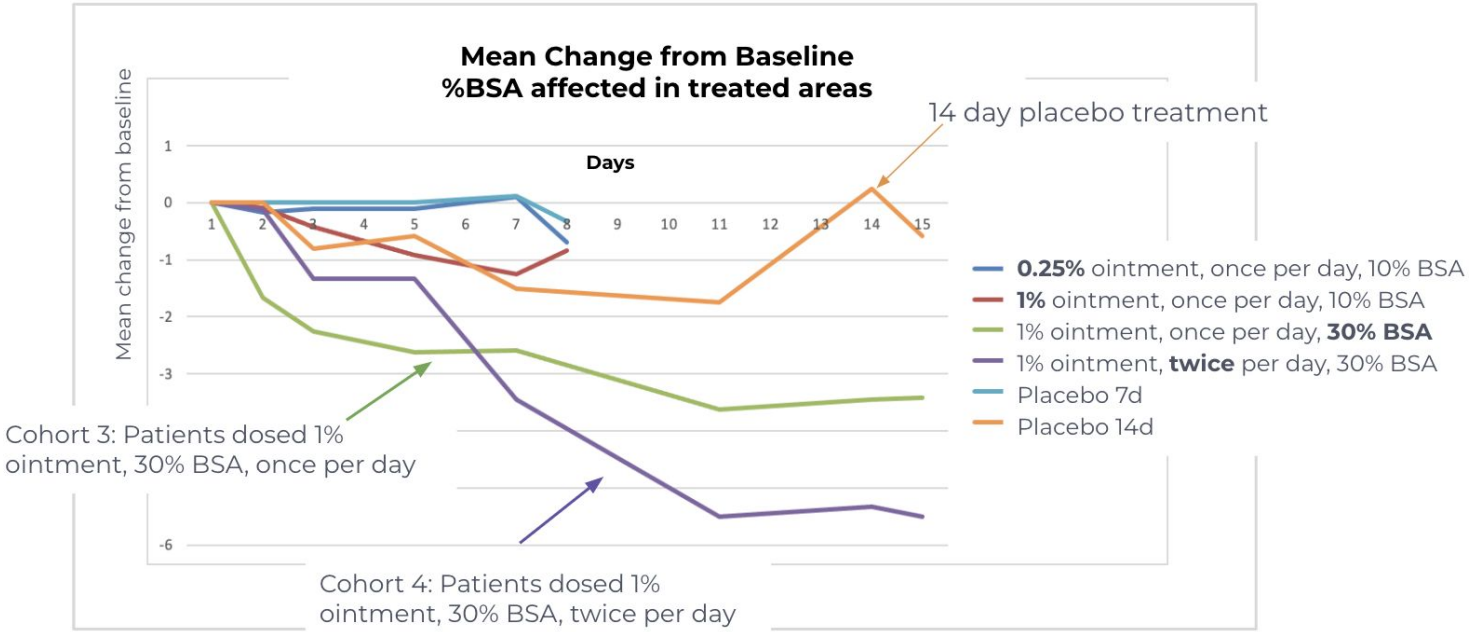
BSA= Body surface area. QD = once per day dosing BID= twice per day dosing

BEN-2293 - indicative data from Phase Ib

Eczema Area and Severity Index (EASI)

Caveats:

- Phase Ib was **NOT** powered to meaningfully assess efficacy - only 6 patients dosed with active per group
- Maximum duration of dosing 14 days (EASI score changes typically measured at 28 days)

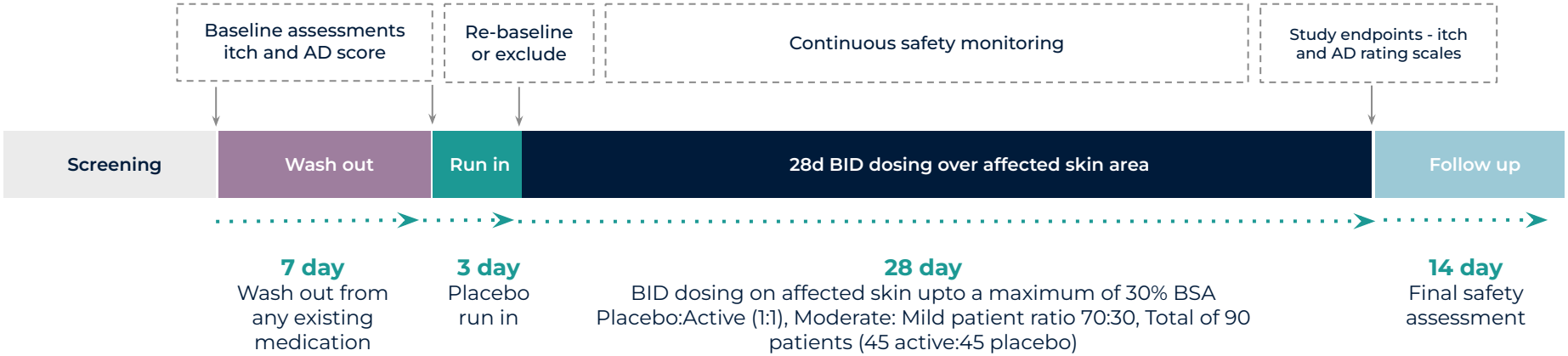


EASI: Eczema Area and Severity Index

BEN-2293 - Phase IIa progressing

Phase Ib/IIa double-blind, placebo-controlled, first-in-patient, two-part clinical study

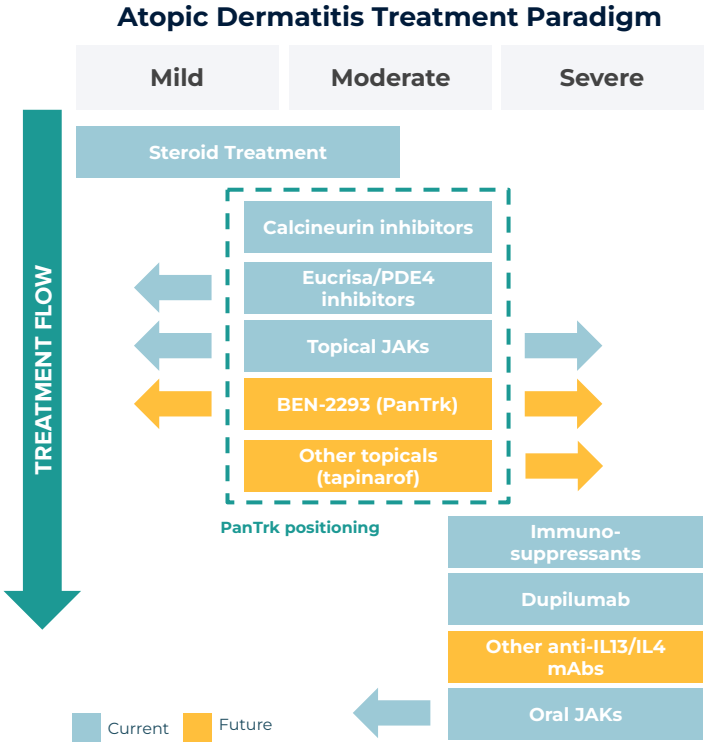
Phase IIa clinical study design



- **11 active recruiting sites,** 7 in the UK, 4 in Europe. A further 17 sites under final approval
- **Recruitment completion** anticipated 4Q22

Our intention is to to partner this asset with a pharmaceutical company that has a focus in dermatology for continued clinical development and, if approved, commercialisation

BEN-2293 is being developed to address key unmet needs in the treatment of Atopic Dermatitis



BEN-2293 development is targeting:

- **Efficacy** against both itch and inflammation, with potential disease modifying effects
- **Improved safety** profile, suitable for chronic use with no irritancy on application

Positioning:

- Potential to **displace ineffective and poorly tolerated second line** treatment for chronic use in adults and paediatrics
- Potential use in a subset of **first line patients where rapid itch resolution is key** and
- In the **severe patient population as an adjunct treatment option**

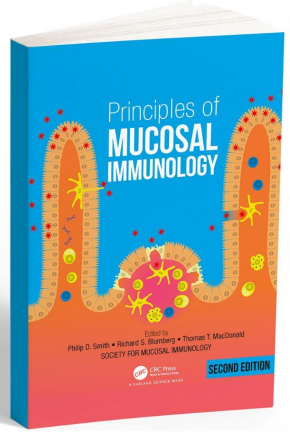
Thomas T MacDonald PhD FMedSci

Professor of Immunology

Barts and the London School of Medicine and Dentistry, QMUL

INTERESTS

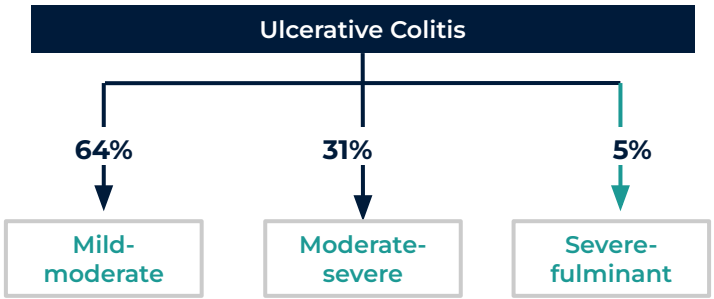
Mucosal immunology and inflammation in man



Ulcerative Colitis (UC)

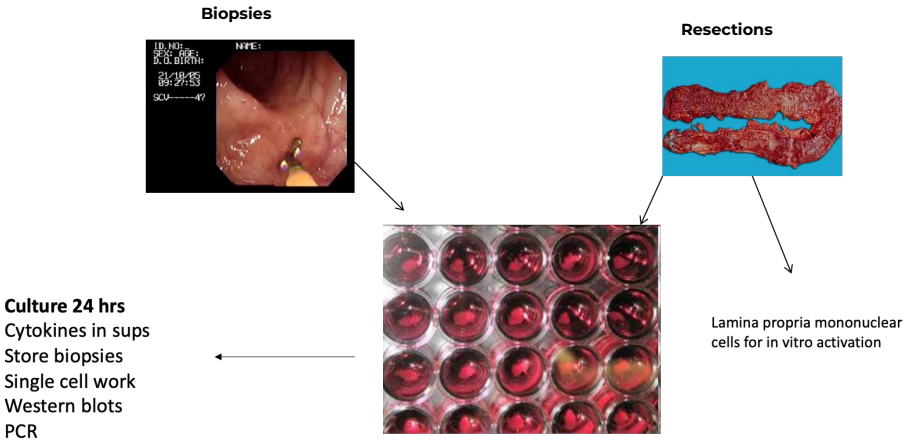
Affects 0.4% US population[1], 1.7 million patients in 7MM[1], forecast $7.8bn market by 2026[2]

- **A chronic, lifelong disease** that causes inflammation and ulceration of the inner lining of the colon and rectum
- **Efficacy** - 20-40% of Moderate-severe patients do not respond to anti-TNF (main treatment paradigm)[3]
- **Safety** - Treatments have many side effects — from steroids to anti-TNF and JAK inhibitors (black box warnings)[4]
- High unmet need for an alternative **oral** small molecule treatment option with **improved safety profile** and efficacy in treatment of r**efractory patients**



Experimental Model System: Inflamed colonic mucosa biopsies from UC patients

- Disease phenotype retained with high basal cytokine release
- Readouts: IL6 and IL8 - key mediators of UC pathology
- Efficacy demonstrated with standard of care therapies

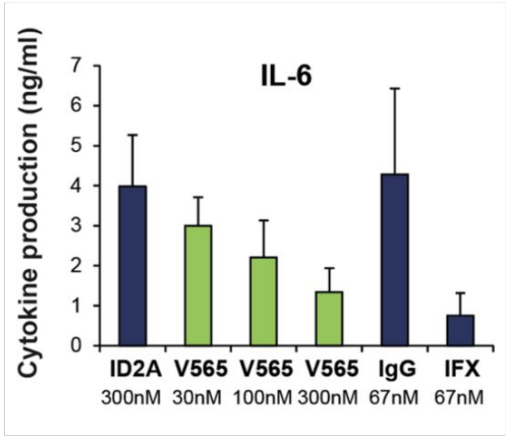


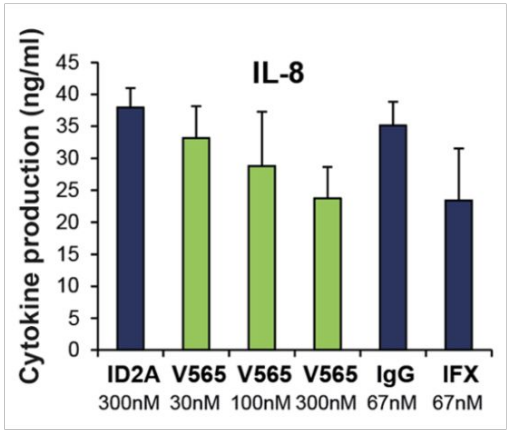
- Short term organ culture of human intestinal mucosa
- Gut is a tissue that is sampled a lot
- Inflamed biopsies do not know that they are not in the gut

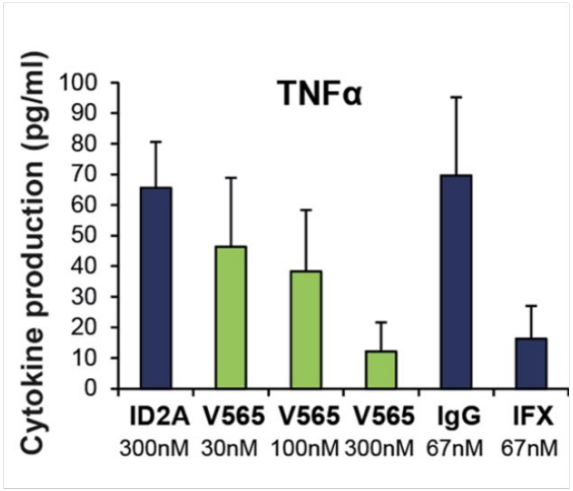
Sources: (1) GlobalData: Ulcerative Colitis, Global Drug Forecast and Market Analysis to 2026; (2) Evaluate Pharma: Gastro-intestinal, Inflammatory bowel disease (IBD), Ulcerative colitis, Worldwide Overview (report 17th Sep 2021); (3) Roda et al. Clin Transl Gastroenterol 2016; (4) Kobayashi et al Nat Rev Dis Primers 2020 and US FDA Drug Safety Communication 2021

Experimental Model System: Inflamed colonic mucosa biopsies from UC patients

- Therapeutic anti-TNF monoclonal antibodies inhibit the spontaneous release of inflammatory cytokines and chemokines in ex *vivo* cultures of inflamed CD and UC tissue.

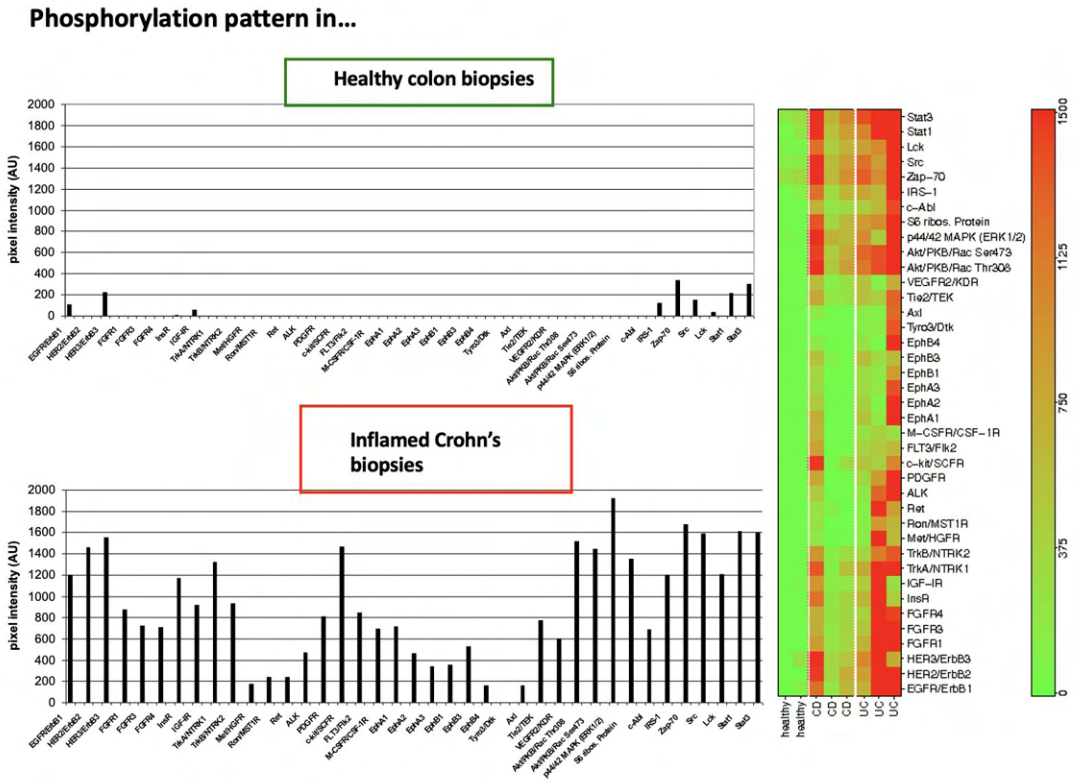




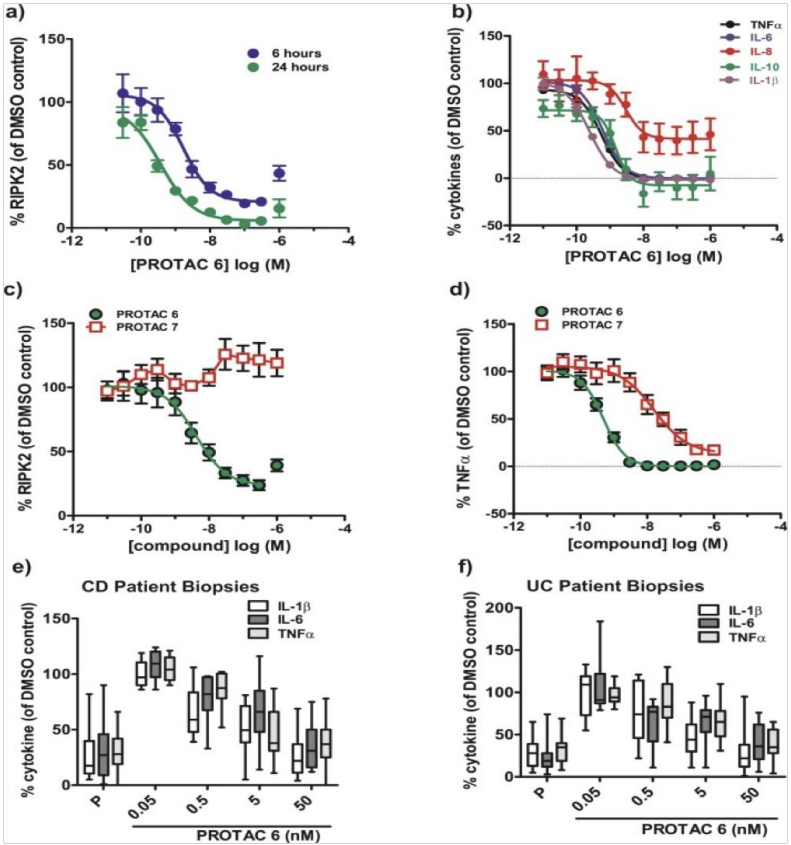


Source: Crowe et al 2018

Colon biopsy signatures



UC and CD biopsies responsive to pharmacological intervention



UC Target Identification workflow

Target Identification

1 Biological Question

Disease — Sign

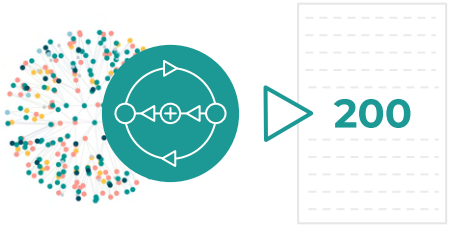
Mechanism

Can we treat UC by reversing chronic inflammation of the colonic mucosa by targeting pathways in colon epithelial cells and tissue resident immune cells?

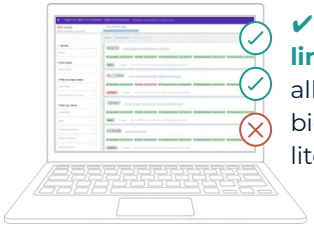
Cell type

Endpoint:
What we will measure

2 Predictive algorithms ran over the curated knowledge graph to identify potential targets, aggregate findings and present the most relevant ones to DD scientists



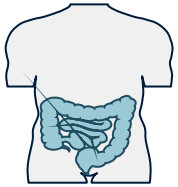
3 Target assessment and validation tools presented scientific evidence allowing scientists to evaluate the rational and opportunity for progressibility



✔ PDE10 has **zero linkage to UC** in all available biomedical literature

4 Experimental validation

Endoscopic Biopsy from UC patients



Colonic mucosa tissue culture and compound treatment

Inflammatory cytokine measurement

PDE10 inhibition promoted an anti-inflammatory effect

BEN-8744 - Phosphodiesterase 10 (PDE10) - a novel target for UC

Transcriptomics data support the rationale for PDE10 as a novel target for UC

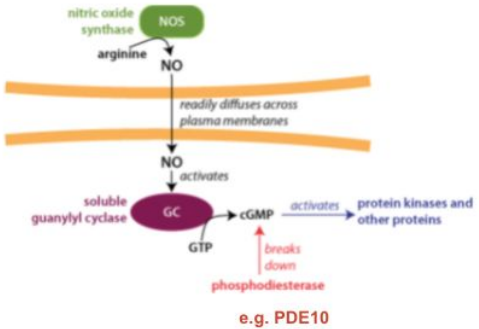
- PDE10 regulates signal transduction by hydrolysing cGMP
- PDE10 is significantly upregulated in UC-derived colon and colonic mucosa samples, whilst guanylyl cyclase, which makes cGMP, is down-regulated

Reduced levels of guanylyl cyclase correlate with increased TNF-α in UC colonic mucosa[1]

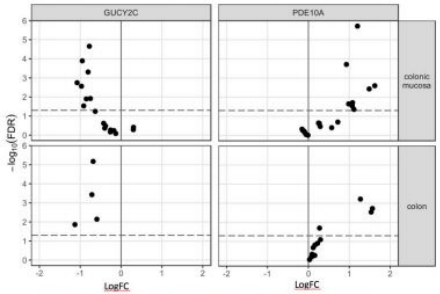
- cGMP is downregulated in UC and its expression inversely correlates to disease severity
- PDE10 is well-studied in CNS disorders but not in inflammation with zero linkage to UC

PDE10 demonstrates restricted expression in peripheral tissue

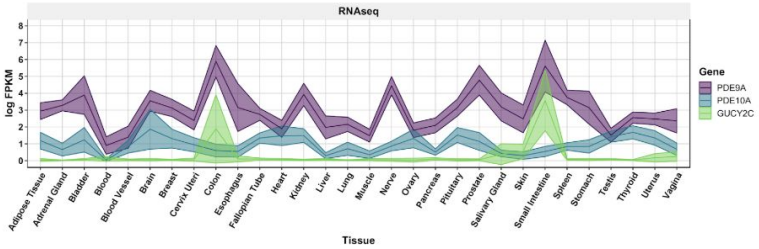
- Reduces the safety liability of targeted inhibition



PDE10 degrades cGMP



Differential RNA expression of PDE10A and GUCY2C: normal vs UC



Low basal PDE10 expression, highest levels in brain. Low basal soluble guanylate cyclase (GUCY2C) levels except in colon and sm intestine

Source: (1) Brenna et al. Scand J Gastroenterol 2015
Image (left): Rashed, Second Messenger System 2018

Target validation in colon tissue from ulcerative colitis patients

Inflamed colonic mucosa biopsies from UC patients

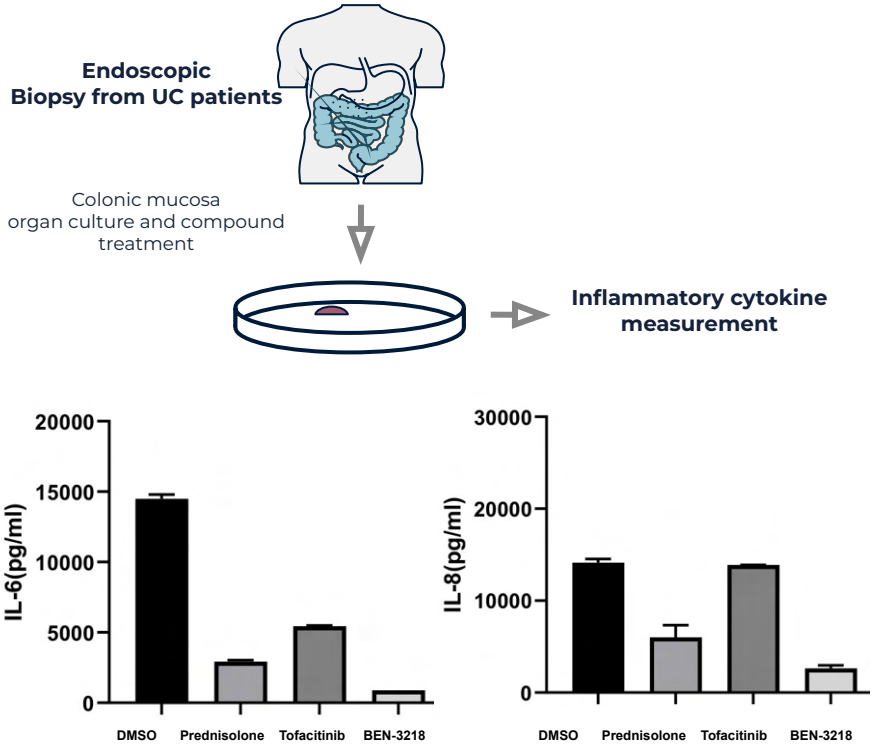
- Disease phenotype retained with high basal cytokine release
- Readouts: IL6 and IL8 - key mediators of UC pathology

Tissue samples treated with:

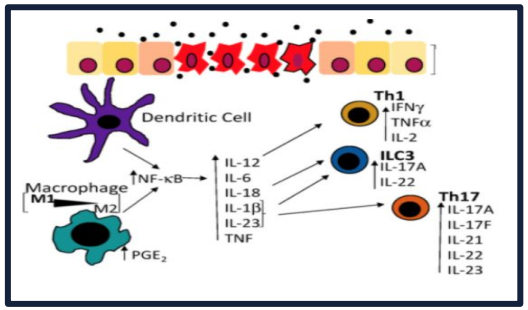
- Target-selective tool compound (BEN-3218)
- Positive controls – prednisolone and tofacitinib

Selective target inhibition showed comparable reduction of IL-6 and IL-8 to the positive controls

Validated as a target with a novel mechanism of action for ulcerative colitis

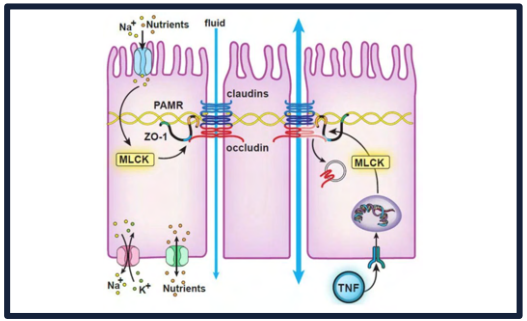


PDE10 inhibition: potential to normalise dysregulated mechanisms in IBD



PDE10 inhibition

↑cGMP ↑cAMP



- Reduced inflammatory cytokine release from intestinal epithelia via ↓NFκB[1]
- Reduced tissue-resident macrophage activation[1]

Reduced intestinal inflammation

- Improved TJ assembly via PKG/PKA-mediated ↓pMLC[2]
- Improved fluid/mucus homeostasis via PKG phosphorylation of intestinal CFTR[3]

Improved barrier integrity

Sources: (1) Harmel-Laws et al PLoS One 2013: (2) Han et al PLoS One 2011; (3) Brenna et al Scand J Gastroenterol 2015
Images: Nettleford and Prabhu, Antioxidants 2018 (left); He et al. Int J Mol Sci 2020 (right)

BEN-8744 results and progress to date

TARGET IDENTIFICATION

Novel target for UC

✔ Discovered using Benevolent **TargetID tools**

✔ PDE10 has **zero linkage to UC** in all available biomedical literature

✔ Experimentally **validated in ex-vivo** UC colon samples from patients refractory to SoC treatment

CHEMISTRY

Rapid and efficient lead optimisation

✔ **Molecular Design tools** enabled rapid and efficient lead optimisation

✔ **Candidate nominated in Sep '21** Novel, potent, selective,peripherally restricted PDE10. Inhibitor, with low dose prediction

✔ Only **2 years** from programme initiation

CLINICAL DEVELOPMENT

Developing responder and progression endotypes

✔ We will develop responder and progression endotypes**, adding molecular descriptors**

✔ These will inform our trial design, **patient selection** and further target identification in UC

✔ Augmenting a further loop of iteration on an enriched graph

BEN-8744 - Best-in-class, oral, peripherally restricted potent and selective drug for the treatment of Moderate-Severe UC

- **Phosphodiesterase 10 (PDE10)** was identified by our TargetID platform as **an entirely novel target for the treatment of UC/IBD**
- Using our Molecular Design expertise we optimally designed a best in class peripherally restricted PDE10 inhibitor: **BEN-8744**
- **BEN-8744** is expected to provide an efficacious disease modifying oral treatment for UC/IBD
- **BEN-8744** will target **Moderate and Severe UC/IBD patients**, meeting the unmet need left by existing therapies including:
  - Patients refractory to anti-TNFs or other biologics
  - Improved safety and tolerability profile compared to competitors
  - A Precision Medicine approach to target key responder patient cohorts, avoiding the safety risks associated with ineffective therapies

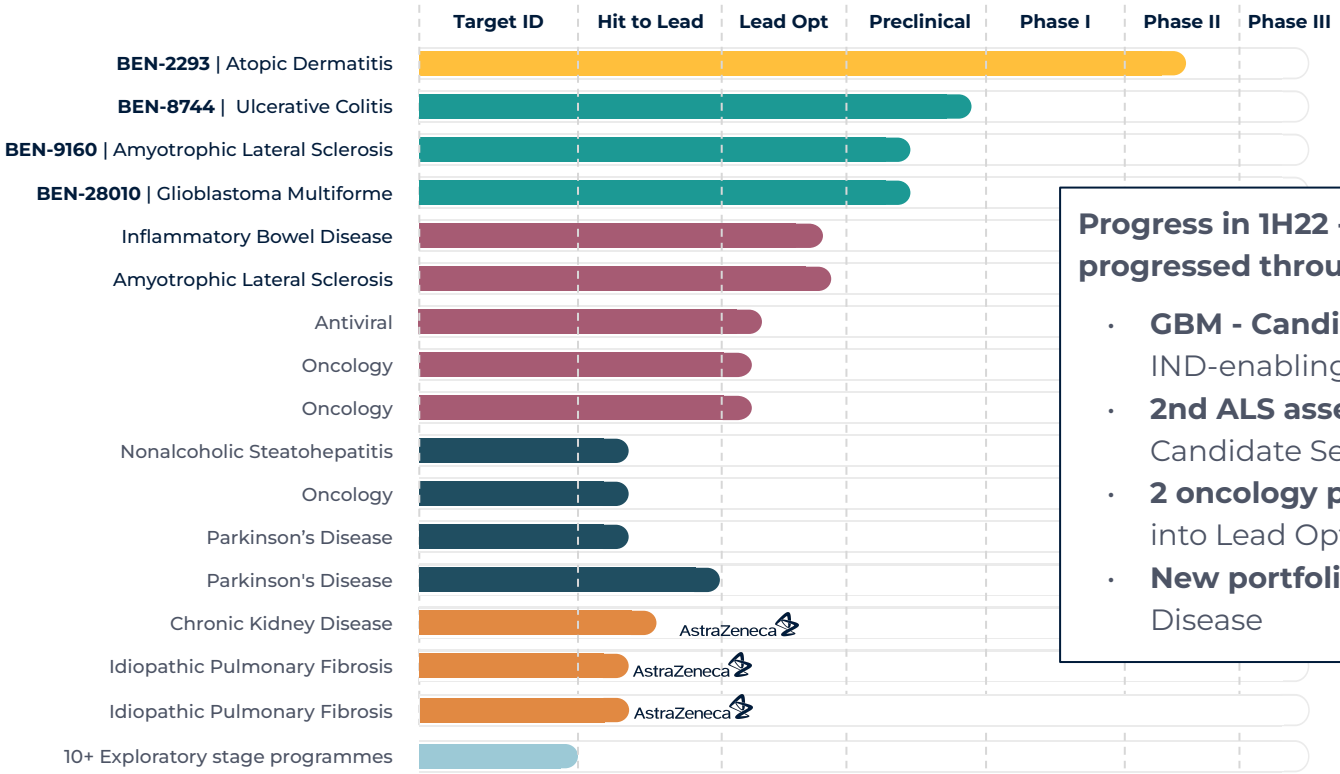
An opportunity to differentiate on safety, efficacy and a precision medicine approaches

Drug	Company	MoA
Zeposia (Ozanimod)	BMS	S1P1 receptor agonist
Etrasimod	Arena	S1P1 receptor agonist
Jyseleca (Filgotinib)	Galapagos & Gilead	JAK1 inhibitor
Rinvoq (Upadacitinib)	Abbvie	JAK1 inhibitor
TD-1473	Theravance & Janssen	Pan-JAK inhibitor (gut-selective)

Safety

- S1P1 agonists are associated with immunosuppression and anaemia
- JAK inhibitors carry a black box health warning

Internal Pipeline - continued progress



Progress in 1H22 - several programmes have progressed through key DD stage gates

- **GBM - Candidate nominated**, IND-enabling studies to begin
- **2nd ALS asset** - transitioned through to Candidate Seeking
- **2 oncology programmes** - transitioned into Lead Optimisation
- **New portfolio entrant** for Parkinson's Disease

Our Precision Medicine approaches are applied to multiple stages of our pipeline and can support repurposing activities

Precision Medicine enabled Target ID

Indication mapping

Additional indications

Repurposing a target or drug (approved or in development) through the identification of additional disease indications

- ✔ Address additional unmet need
- ✔ Maximise the value of a target or drug programme

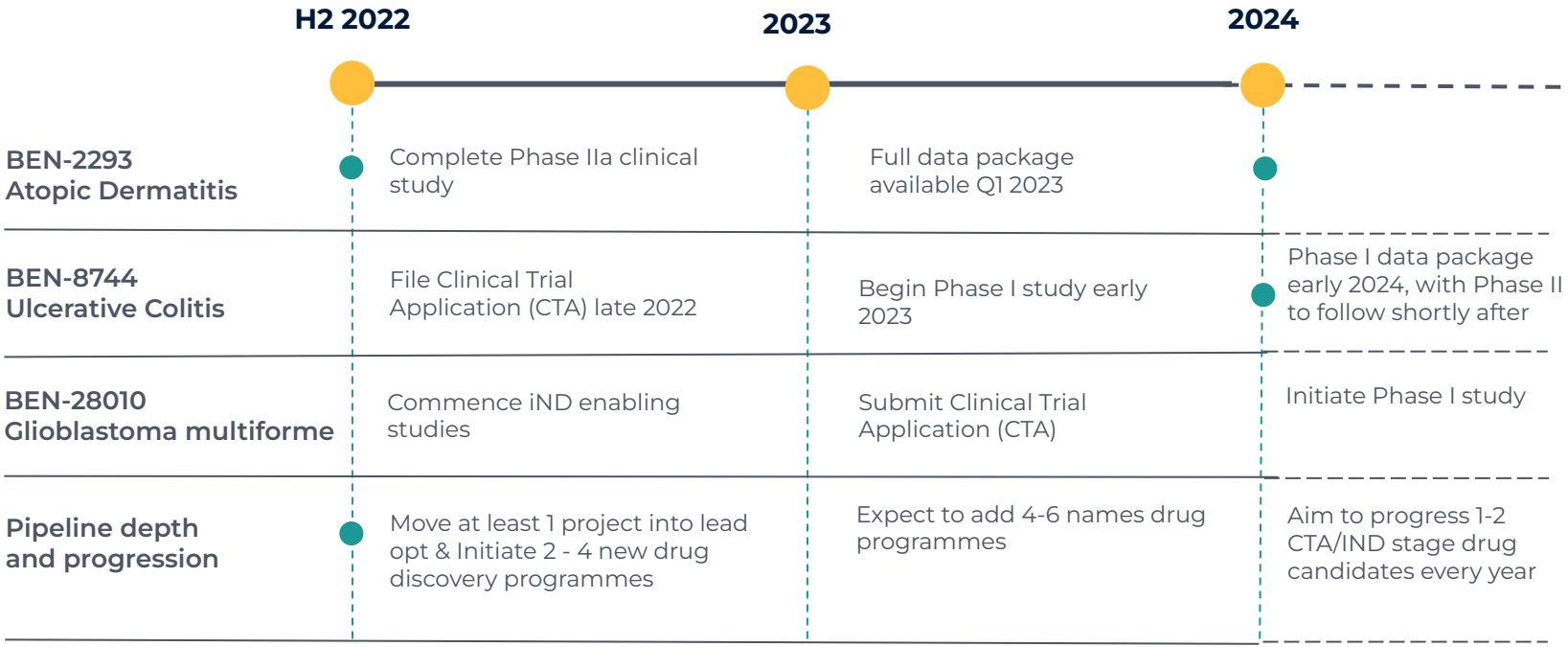
Identifying key patient cohorts and responders for drugs

- ✔ Optimise clinical development
- ✔ Increase probability of success
- ✔ Improve outcomes for patients

Identification of patient cohorts & responders

Optimised trial design & patient outcomes for each indication

Portfolio key inflection points



Interim Results - H1 Operational & Financial Review

6 months ended 30 June 2022

Nick Keher, CFO

Benevolent AI

H1 2022 Highlights

1. Continued progress across in-house pipeline
2. Consistent delivery in collaboration with AstraZeneca - non-commercial collaborations progressing
3. Full FDA approval of COVID-19 treatment first identified by BenevolentAI
4. Continuous enhancement of the Benevolent Platform™
5. Completed Business Combination/listed Amsterdam EuroNext - raised gross proceeds of €225m
6. Strengthened Board of Directors and Leadership
7. Building Business Operations capability for long term success

1H 2022 Financial highlights

	Six months ended 30 June	
	2022	2021
	£'000	£'000
Revenue	4,843	1,664
R&D - Drug discovery ["DD"][1]	(19,292)	(12,957)
R&D - Product & technology ["P&T"][1]	(10,684)	(9,940)
G&A - Business operations ["Bus Ops"][1]	(8,074)	(7,000)
Underlying expenses related to share-based payments	(22,145)	(18,343)
Other income	72	74
Normalised operating loss	(55,280)	(46,502)
Normalised EPS (in pence)[2]	(44.7)	(45.8)
Weighted average ordinary shares outstanding (in millions)	100.5	89.8

Revenue increase across AstraZeneca collaboration, with a milestone reached related to the second novel target for idiopathic pulmonary fibrosis.

DD spend increase driven by portfolio advancing into later stages of development, in particular BEN-2293 entering adaptive Phase I/II clinical study.

P&T spend increase reflecting increased headcount, which is set to plateau.

Bus Ops spend +15%, driven predominantly by listing status but expected to maintain at this level.

1) Excludes exceptional costs related to the Business Combination
2) Normalised EPS also excludes taxation impact from exceptional items and finance income related to the Business Combination

Walk from Reported to Normalised[1]

	Six months ended 30 June	
	2022	2021
	£'000	£'000
Reported operating loss	**(134,547)**	**(46,502)**
Adjustments for:		
G&A - Exceptional share-based payment ("SBP") expenses	2,611	-
G&A - Direct Transaction costs	11,255	-
G&A - Non-cash listing service expense	65,401	-
Normalised[1] group operating loss	**(55,280)**	**(46,502)**

Reported loss significantly driven by non-recurring costs of Business Combination.

Non-cash exceptional costs related to acceleration of share based payments also incurred from Business Combination, and set to reduce beyond 2022.

Non-cash listing service expenses reflects cost of share issuance to Odyssey SPAC as part of Business Combination net of assets acquired (before PIPE and backstop)

1) Excludes exceptional costs related to the Business Combination

Cashflows focused upon drug and platform development

	Six months ended 30 June 2022 £'000
Normalised[1] operating loss	(55,280)
Depreciation & amortisation	1,506
Foreign exchange	(1,589)
Equity share-based payment	21,913
Cash flows from changes in working capital	(12,312)
Cash expended from underlying operating activities	(45,762)
Opening cash balance	40,553
Closing cash balance	165,338

£0.3m lab equipment; £0.1m computer; £1.1m property-related leases

£3m charge from Euro holdings, £1.8m gain from operational

Non-Transaction-related equity awards removed from the P&L (no cash impact)

Largely driven by outstanding R&D tax credit receivable (£12m) expected in 2H and other payable decreases

End-June cash position of £165.3m provides ample liquidity to meet multiple key value inflection points

1) Excludes exceptional costs related to the Business Combination

Cash runway to Q4-2024 providing sufficient capital for key value inflection points

Cash Runway

Cash at 30th June 2022	£165m
H2 2022 cash spend	£36m-£40m

BEN-2293 trial costs (c.£15m) fall away in 2023

Cash runway guidance assumes no future capital from licensing or collaboration agreements

Multiple assets at or close to key value inflection points and ready for out-licensing

Capital allocation

Closing Remarks and Outlook

Joanna Shields, CEO

Benevolent AI

Benevolent[AI] • Investment Highlights

- Market leader in AI drug discovery with scientifically and technologically differentiated approach
- Robust IP with patents on drug pipeline and copyright and trade secrets on our technology platform
- Significant platform scale and internal capability
- Flexible business model with revenue opportunities to extend cash runway
- Rich portfolio of drug programmes all generated from the Benevolent Platform™
- Near and medium-term key value inflection points
- High-value and successful commercial partnership proving strategic validation
- World-renowned Board and experienced leadership team

Poised for growth and success

Strengthened financial position enhances our leadership position in AI-enabled drug discovery and enable us to:

✔ **Independently pursue the clinical development** of certain **in-house pipeline** assets in core therapeutic areas

✔ **Out-license multiple assets** over the next 1-3 years to strengthen our balance sheet and drive long term value creation

✔ **Increase the size of our pipeline** with a healthy balance of new first-in-class and best-in-class assets with 1-2 CTA / IND-stage drug candidates every year

✔ **Sign new collaboration agreements** with pharma companies to to leverage our disease agnostic capabilities into therapeutic indications outside our focus areas, to generate incremental revenue

✔ **Maintain our leading position in Target ID** through increased investment in our technology capabilities

✔ **Build out our technology metrics** to exemplify the differentiation of our approach

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