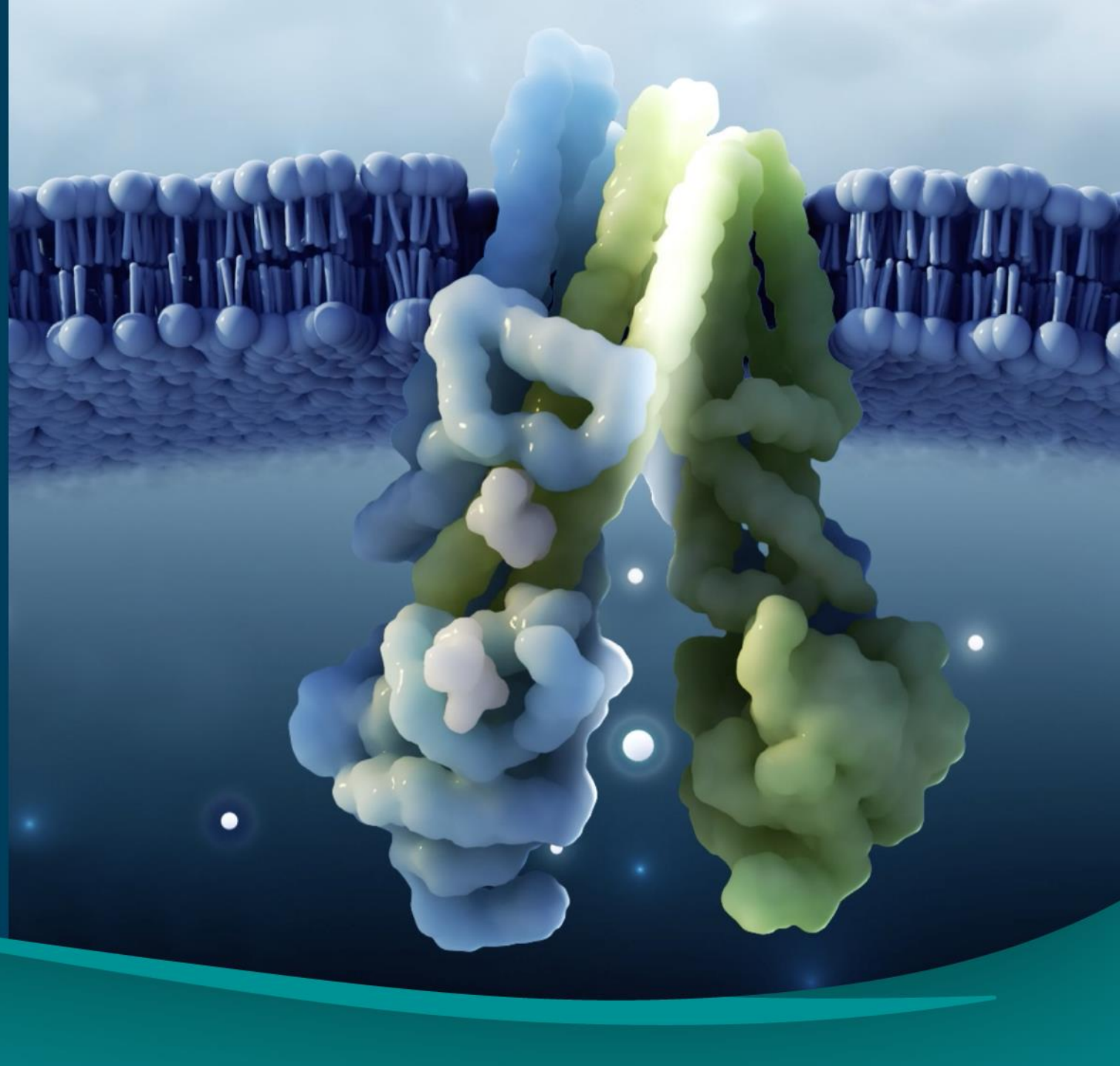
Mike Cloonan, President & CEO

42nd Annual J.P. Morgan Healthcare Conference

January 2024



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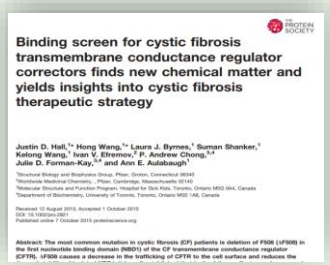
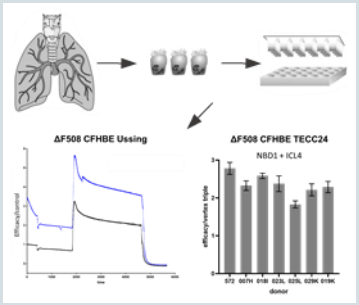
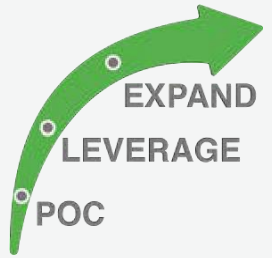
Sionna's differentiated approach focused on NBD1 has a clear path to POC with the potential to deliver best-in-class efficacy

HIGH UNMET NEED IN LARGE MARKET	NBD1, THE HOLY GRAIL FOR CFTR	PREDICTIVE ASSAYS/BIOMARKERS	FRANCHISE DRIVES STRATEGIC OPTIONALITY
			
Despite current treatments, unmet need is high in the $10B market	**NBD1 is the key to deliver full CFTR function and has been considered 'undruggable'**	**CFHBE assay and sweat chloride biomarker consistently predict clinical efficacy driving near-term value inflection**	**A deep pipeline of NBD1 compounds and complementary modulators can significantly raise the efficacy bar**

Led by proven management capable of disrupting the CF market

Mike Cloonan
Chief Executive Officer

Sage Therapeutics™ · Biogen · BAIN & COMPANY

Charlotte McKee, MD
Chief Medical Officer

VERTEX · Infinity PHARMACEUTICALS · TOLERX Immune resolve. · Wyeth

Brigham and Women's Hospital
Founding Member, Mass General Brigham

Elena Ridloff
Chief Financial Officer

ACADIA · ALEXION

Greg Hurlbut, PhD
Co-Founder
SVP, Discovery Research

sanofi genzyme

Vanya Sagar
Chief People Officer

Affinivax · sigilon therapeutics · Biogen

Mark Munson, PhD
Co-Founder
VP, Medicinal Chemistry

sanofi · AMGEN · ARRAY

John Macor, PhD
Chair, SAB

sanofi · Pfizer · Bristol Myers Squibb™

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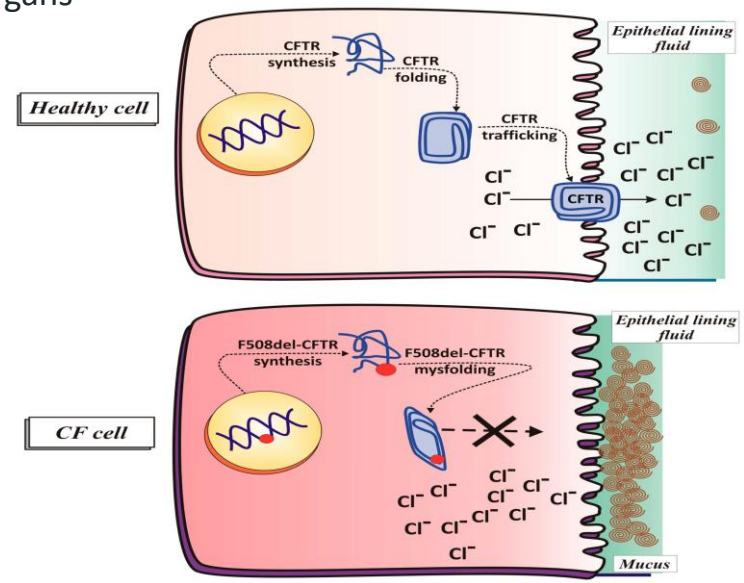
CFTR is a fully validated target, and unlocking NBD1 could deliver optimal clinical benefit in CF

The Biology of CF

- Driven by mutation of the CF transmembrane conductance regulator (CFTR)
- CFTR is an epithelial chloride channel essential to the production of thin, freely flowing mucus in the airways, digestive system, and other organs



The Importance of NBD1

- F508 is present within CFTR's NBD1 domain
- ΔF508 causes NBD1 to unfold at body temperature and weakens NBD1's interface with other regions; these defects cripple CFTR folding, trafficking and function
- **<u>None</u> of the existing correctors or potentiators address both ΔF508-CFTR's assembly and its NBD1 instability defects**
- ~90% of patients with CF have a ΔF508 mutation

NBD1 is the key to full CFTR correction

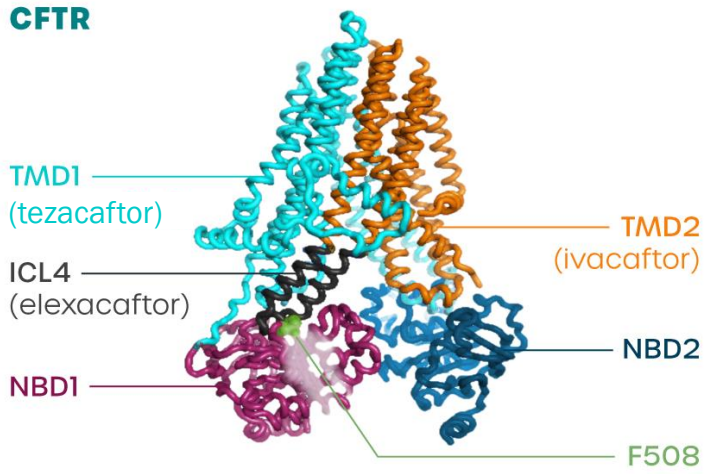


Image Source: J. Clin. Med. 2019, "An Intriguing Involvement of Mitochondria in Cystic Fibrosis"

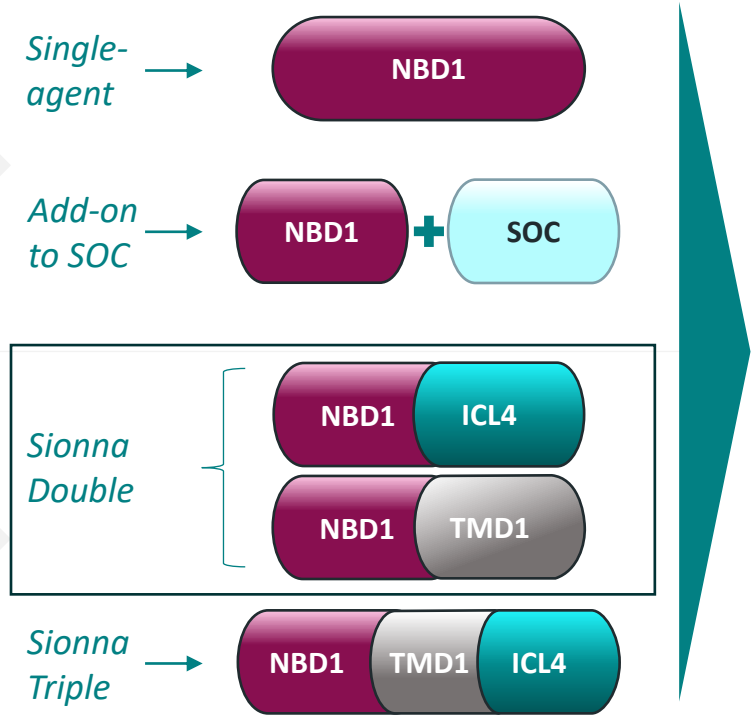
Sionna's strategy is to build a CF franchise across MOAs, anchored by novel NBD1, delivering higher efficacy than SOC

NBD1

Drive multiple NBD1 compounds into the clinic, advance based on human data and the potential to raise the efficacy bar

NBD1 + ICL4 / TMD1

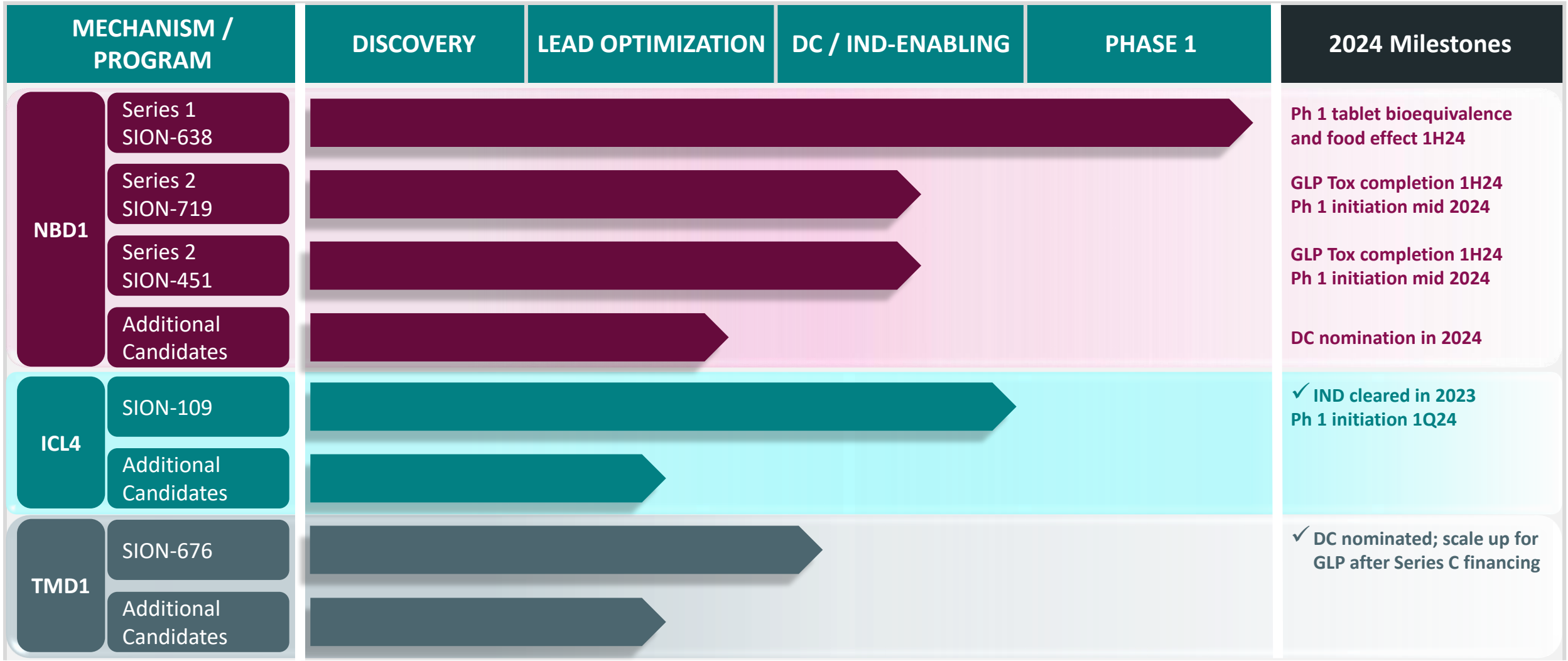
Accelerate pipeline of complementary targets creating options for transformational Sionna combinations with NBD1



Targeting Efficacy ≥ SOC

Vision: Deliver transformational option to fully normalize CFTR function, become the SOC

Sionna is advancing a robust pipeline with multiple near-term clinical milestones



Three NBD1 ‘shots on goal’ increases probability of success for clinical PoC and will ensure we take our best shot first

	SION-638	SION-719	SION-451
Potential Use Case	**Trikafta add-on** ‘638 + SOC	**Sionna Double** ‘719 ‘109	**Sionna Double** ‘451 ‘109
POC Predicted Dose	Optimal dose identified	Projected low doses	Projected low doses
Target Clinical Exposure (based on CFHBE model)	Achieved target exposure in Ph 1 SAD/MAD	Projecting significantly lower target exposure vs. ‘638	Projecting significantly lower target exposure vs. ‘638
Extrapolated Efficacy (compared to TRIKAFTA®)	Potential improvement of 10mEq SwCl and 3-5 pp FEV_1	Potential improvement of >20mEq SwCl and >5 pp FEV_1	Potential improvement of >20mEq in SwCl and >5 pp FEV_1
Path to Phase 2a	Advanceable to Ph2a POC; Wait for ‘719 & ‘451 Ph 1 data for decision	Potential better shot on goal with higher potency & efficacy potential	Potential best shot on goal based on higher potency, efficacy and highest pre-clinical safety margins

Review Ph 1 data for all 3 NBD1 compounds and select best compound to advance; take our Best POC shot first to increase POS

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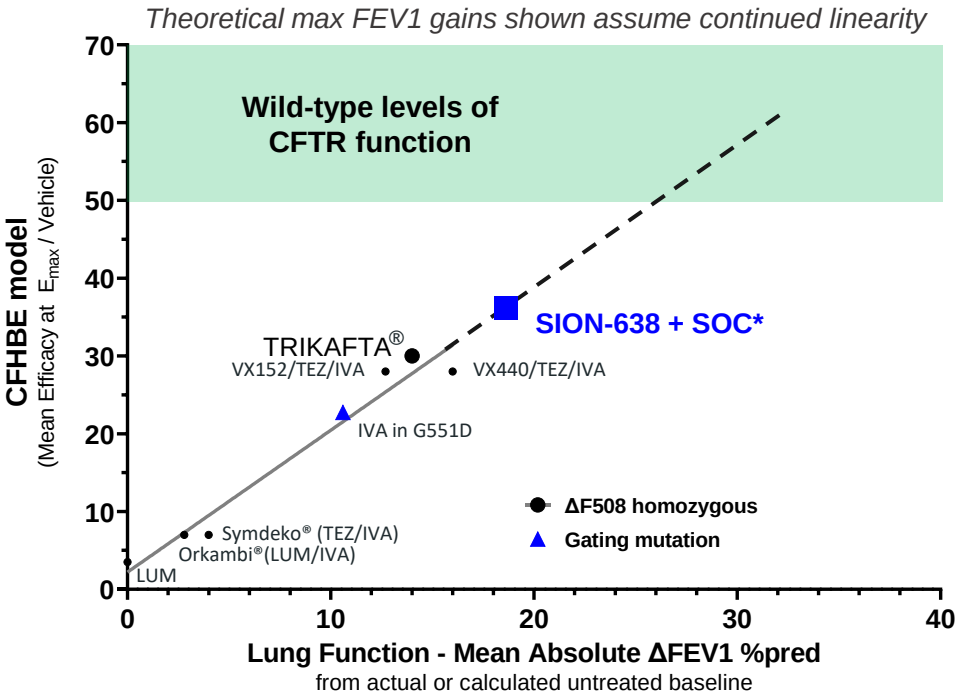
pp – percentage points
*Add-on to SOC has potential higher market share at lower price
Trikafta® is a registered trademark of Vertex Pharmaceuticals

SION-638: First-in-class, clinical stage NBD1 modulator with the potential to deliver higher efficacy

SION-638 CFHBE assay data



Phase 1 human PK supports potential for improved efficacy as an add-on to SOC

- Exposure target for Ph1 was derived from the CFHBE model to drive clinically meaningful efficacy
- Dose identified in Ph1 that achieves target exposure to deliver improved efficacy as add-on to Trikafta®
- Next steps, Ph1 food effect and tablet bioequivalence (1H24)
- Progression to Ph2a will be a portfolio decision as we gather Ph1 data for Series 2 compounds

*Based on SION-638 exposure at target dose
Trikafta®, Symdeko®, and Orkambi® are registered trademark of Vertex Pharmaceuticals

Overview of NBD1 Series 2 development candidates: SION-451 and SION-719

Mechanism of Action	• NBD1 Stabilizer

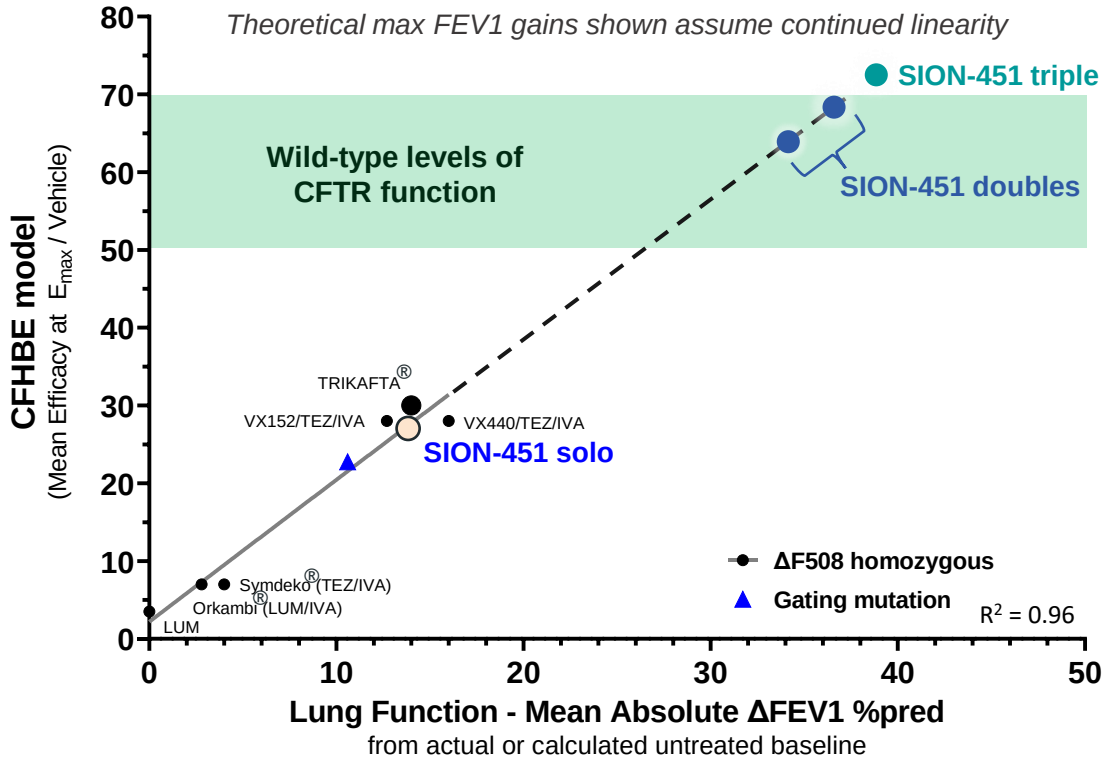
Rationale and Enthusiasm for Advancement	• SION-451 and SION-719:
	  • Potent NBD1 stabilizers with potential to fully correct ΔF508-CFTR in dual combo
	  • Promising drug-like profile, robust clinical efficacy predicted at low doses
	  • Completed exploratory tox with safety profile supporting accelerated advancement
	  • **Based on current data, SION-451 could be the most compelling NBD1 compound**

Status	• DC nominated • In-life portion of GLP tox studies completed
Key Upcoming Milestones	• Complete GLP data packages 1H24 • Phase 1 initiations planned for mid 2024 in Australia • Plan to submit US IND after Ph 1
Preferred Use Case & TPP	• Foundation of a Sionna proprietary dual combos

DC - Development Candidate, GLP - Good Laboratory Practice, ICL4 - Intracellular Loop 4 of CFTR, IND - Investigational New Drug application, MOA - Mechanism of Action, NBD1 - Nucleotide Binding Domain 1 of CFTR, SOC - Standard of Care, TMD1 - Transmembrane Domain 1 of CFTR

SION-451: Series 2 NBD1 development candidate demonstrates potential to normalize CFTR function

Potential of SION-451 at E_{max}



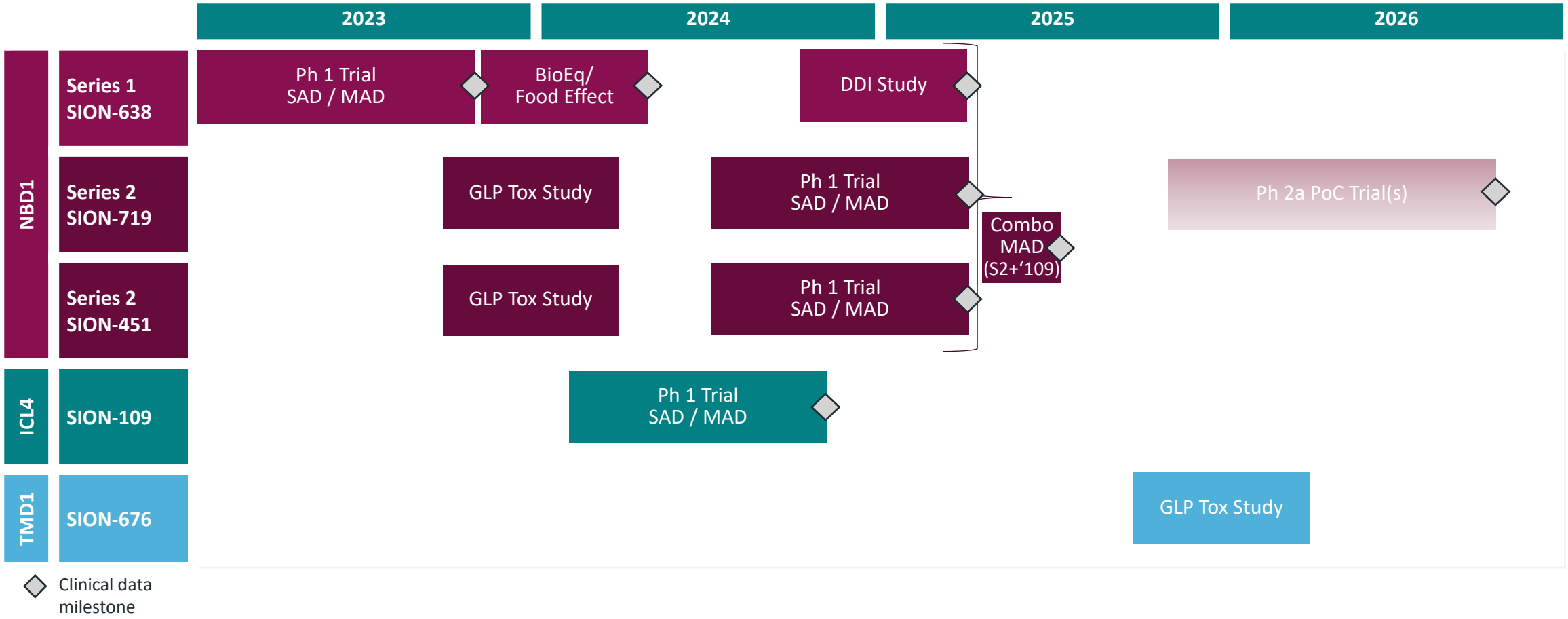
Multiple options to raise the efficacy bar

In the clinically predictive CFHBE assay, SION-451 has demonstrated the potential for:

- Single-agent efficacy equivalent to Trikafta®
- Wild-type levels of CFTR function in Sionna combinations with TMD1 and/or ICL4
- Wild-type levels of CFTR function for SION-451 as add-on to Trikafta

CFHBE - CF Human Bronchial Epithelial primary cells, DC - Development Candidate, FEV- Forced Expiratory Volume, Gating mutation - G551D CFTR, ELX - elexacaftor, IVA - ivacaftor, LUM - lumacaftor, SOC - Standard of Care, TEZ - tezacaftor, Trikafta - ELX/TEZ/IVA.
Trikafta®, Symdeko®, and Orkambi® are registered trademark of Vertex Pharmaceuticals

Three NBD1 programs with Ph 1 data by early 2025 to support portfolio decision to advance best compound to Ph2a



Sionna is well positioned to advance its pipeline

~$150M raised since company founding in 2019

Targeting $80-100M Series C to fund company through 2025

Management team with deep CF and rare disease expertise

RA CAPITAL

TPG

ATLAS VENTURE

OrbiMed
Healthcare Fund Management

CYSTIC FIBROSIS FOUNDATION

Advancing game changing therapies, building significant near-term value, and driving to raise the efficacy bar in CF

DELIVER **ROBUST NBD1 PORTFOLIO**	**SION-638 Phase 1 SAD/MAD completed 2H23** **SION-719 GLP 1H24; Phase 1 initiation mid 2024** **SION-451 GLP 1H24; Phase 1 initiation mid 2024**
ADVANCE **COMPLEMENTARY TARGETS**	**SION-109 (ICL4 candidate); Phase 1 initiation 1Q24** **SION-676 (TMD1 candidate) DC nominated**
BUILD **COMPANY CAPABILITIES**	**Execute the strategy, grow the company and build capabilities to become a leader in CF**

Thank you

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