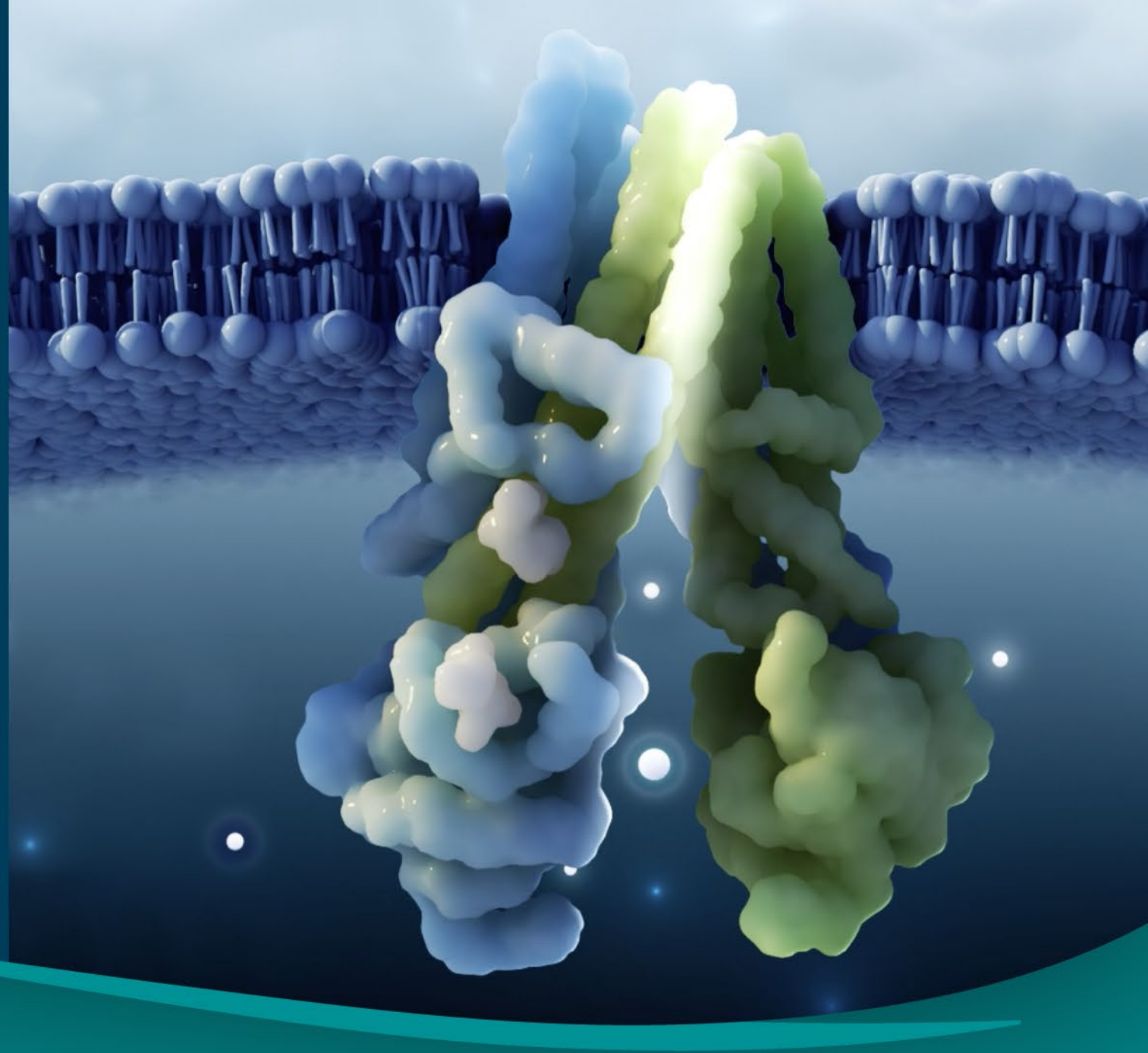
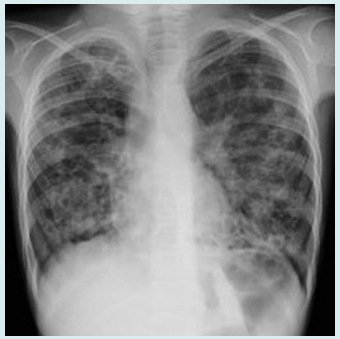
Sionna Therapeutics

August 2024



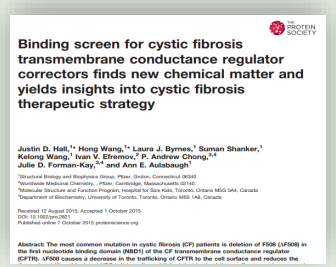
Sionna's differentiated approach focused on NBD1 has a clear path to POC with the potential to deliver best-in-class efficacy

HIGH UNMET NEED IN LARGE MARKET



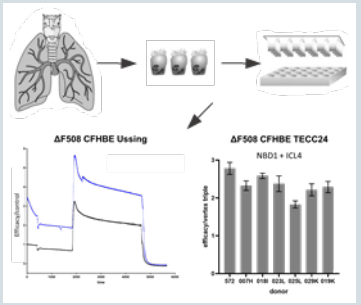
Despite current treatments, unmet need is high in the >$10B market

NBD1, THE HOLY GRAIL FOR CFTR



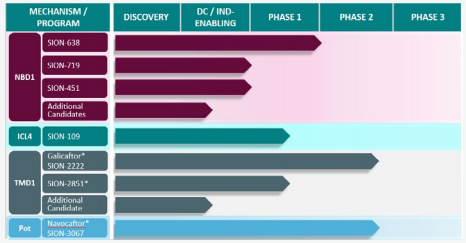
NBD1 is the key to deliver full CFTR function and has been considered 'undruggable'

PREDICTIVE ASSAYS/BIOMARKERS



CFHBE assay and sweat chloride biomarker consistently predict clinical efficacy driving near-term value inflection

FRANCHISE DRIVES STRATEGIC OPTIONALITY



A deep clinical stage 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

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Greg Hurlbut, PhD
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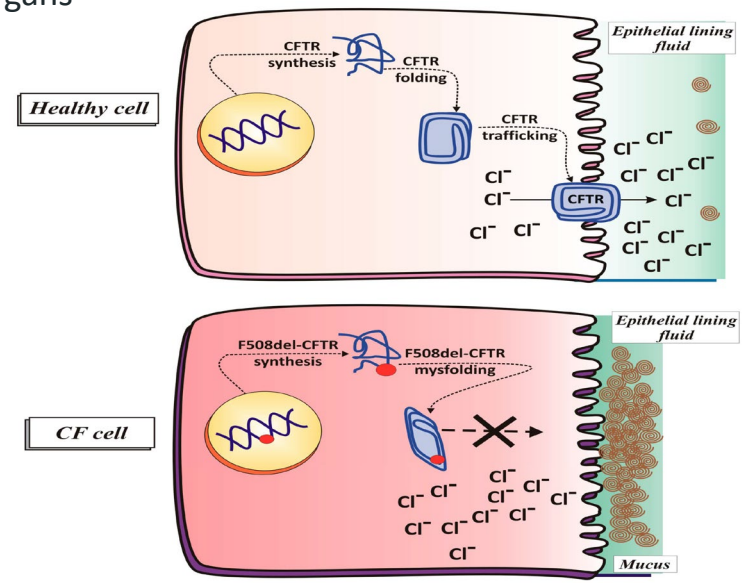
Mark Munson, PhD
Co-Founder
VP, Medicinal Chemistry

sanofi · AMGEN · ARRAY

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
- F508del 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**
- ~85% of patients with CF have a F508del mutation

NBD1 is the key to full CFTR correction

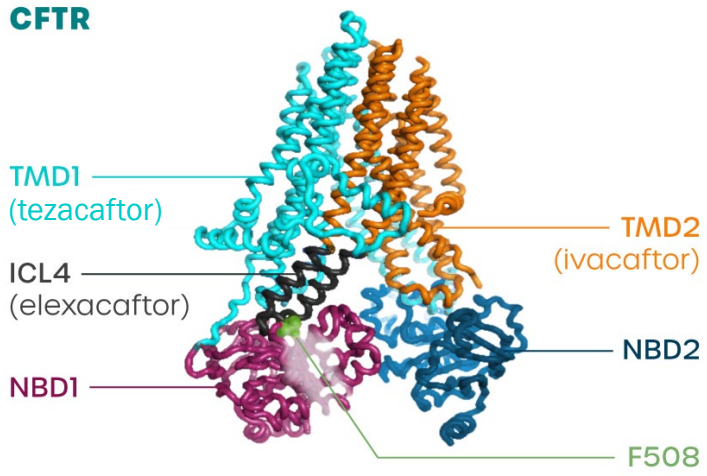


Image Source: J. Clin. Med. 2019, "An Intriguing Involvement of Mitochondria in Cystic Fibrosis"

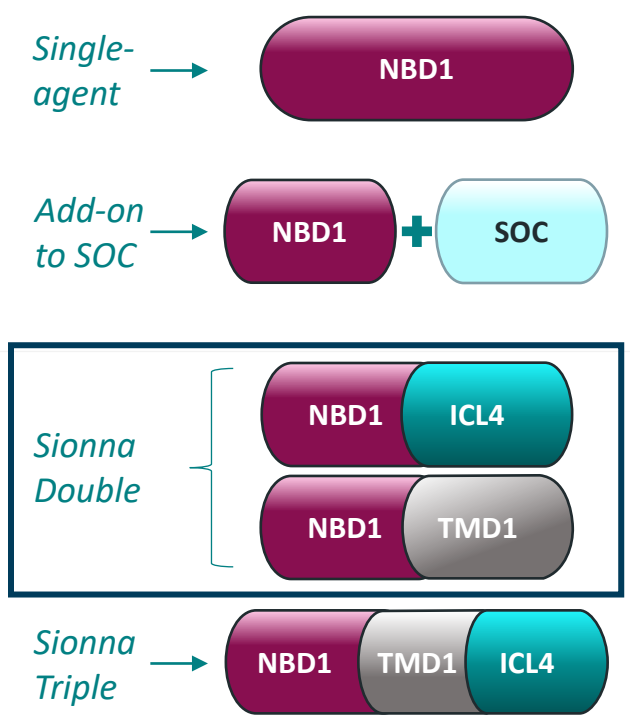
Sionna's strategy is to build a CF franchise across MOAs, anchored by novel NBD1, aimed at delivering higher efficacy than SOC

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

We are well positioned to execute our strategy to deliver transformational CF treatment options and drive near-term value

Well Funded with $182M Series C

- Upsized Series C in March 2024; funds Sionna through YE26 and Ph 2a POC study
- Participation from all existing investors with three new strong investors added to syndicate

RACAPITAL ATLASVENTURE ENAVATE SCIENCES PERCEPTIVE ADVISORS TPG OrbiMed Healthcare Fund Management Viking CYSTIC FIBROSIS FOUNDATION

Proven Execution with Ph 1 Advancement

- SION-638 (NBD1) completed Ph 1 study; compound is advanceable to Ph 2, subject to portfolio decision
- SION-109 (ICL4) Ph 1 ongoing on-track for completion by YE24

Pioneering Next-Gen NBD1 Assets

- Completed GLP tox studies for both next-gen NBD1 compounds, SION-451 and SION-719
- GLP tox demonstrated high margins with no dose limiting toxicity
- Both compounds on-track for Ph 1 initiation in mid-24

Pipeline Expansion with AbbVie Licensing

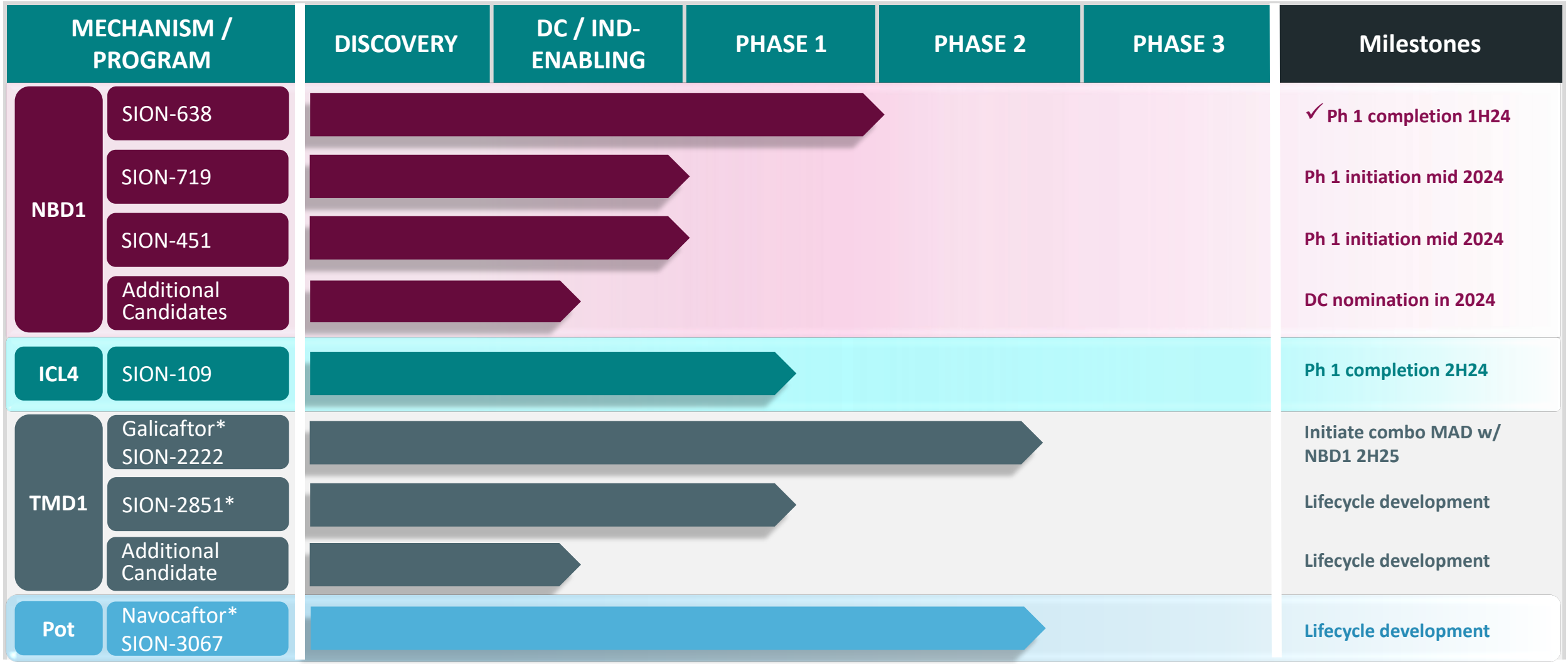
- Exclusive WW rights for three clinical-stage compounds that expand and de-risk the combination options with NBD1
- Select the best dual combination option with NBD1
- Additional clinical assets become lifecycle development opportunities

Licensing the ABBV modulators aims to expand and de-risk Sionna's combo development strategy

Compelling Activity in CFHBE Assay	NBD1 dual combinations with ABBV-2222, ABBV-3067, ABBV-2851, and SION-109 demonstrate the potential for superior efficacy to SOC in CFHBE assay
Accelerated and De-Risked Dual Combo Strategy	Galicaftor (ABBV-2222), a TMD1 modulator, has positive Ph 2 data in CF patients[1] Plan to advance ABBV-2222 and SION-109, if Ph 1 is successful, as potential dual combination options with an NBD1 stabilizer
LCM Options with Additional Clinical Assets	Navocaftor (ABBV-3067), a potentiator, also has positive Ph 2 data; ABBV-2851 is a Ph 1 TMD1 modulator Both modulators provide lifecycle development opportunities

1. ClinicalTrials.gov (June 2023)

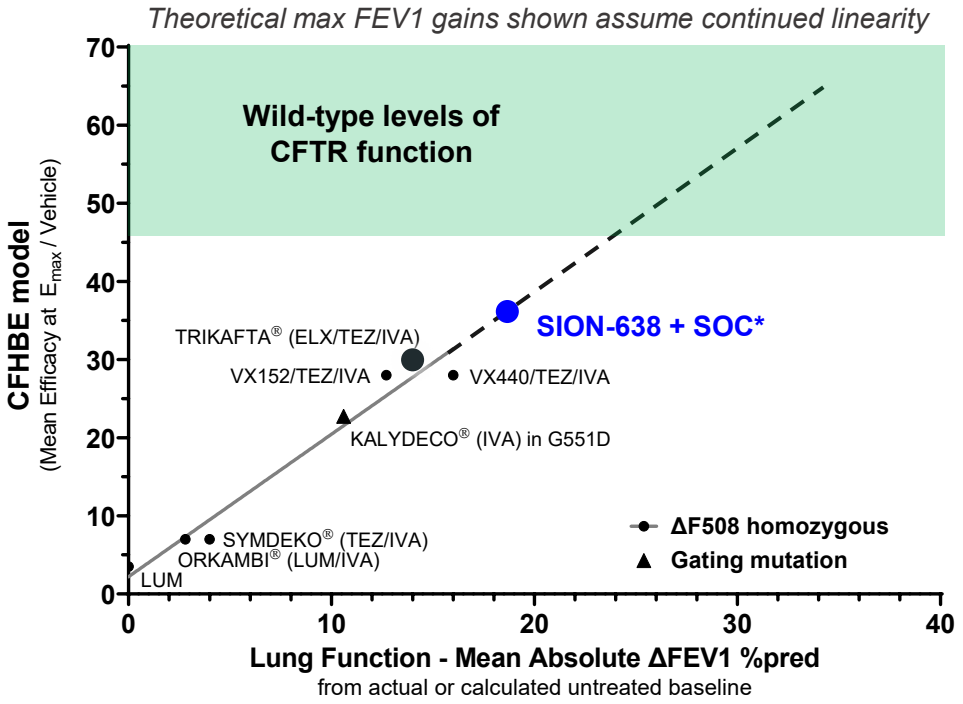
Sionna has a robust pipeline to drive NBD1 combination strategy with several near-term clinical milestones



*Licensed compounds from AbbVie: galicaftor (FKA ABBV-2222), SION-2851 (FKA ABBV-2851), and navocaftor (FKA ABBV-3067)
DC - Development Candidate, GLP - Good Laboratory Practice, ICL4 - Intracellular Loop 4 of CFTR, IND – Investigational New Drug application, NBD1 - Nucleotide Binding Domain 1 of CFTR, Ph 1 - clinical development Phase 1, Pot – potentiator, TMD1 - Transmembrane Domain 1 of CFTR.

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

SION-638 CFHBE assay data



Green horizontal bar: average FSK response +/- standard error of the mean across a panel of 8 non-CF HBE donors.

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

- Exposure target for Ph 1 was derived from the CFHBE model** to drive clinically meaningful efficacy
- Dose identified in Ph 1 that achieves target exposure to deliver improved efficacy as add-on to SOC (Trikafta®)
- Progression to Ph 2a will be a portfolio decision informed by Ph 1 data for SION-451 and SION-719

*Based on SION-638 exposure at target dose
** Source: Pre-clinical assays conducted by Sionna
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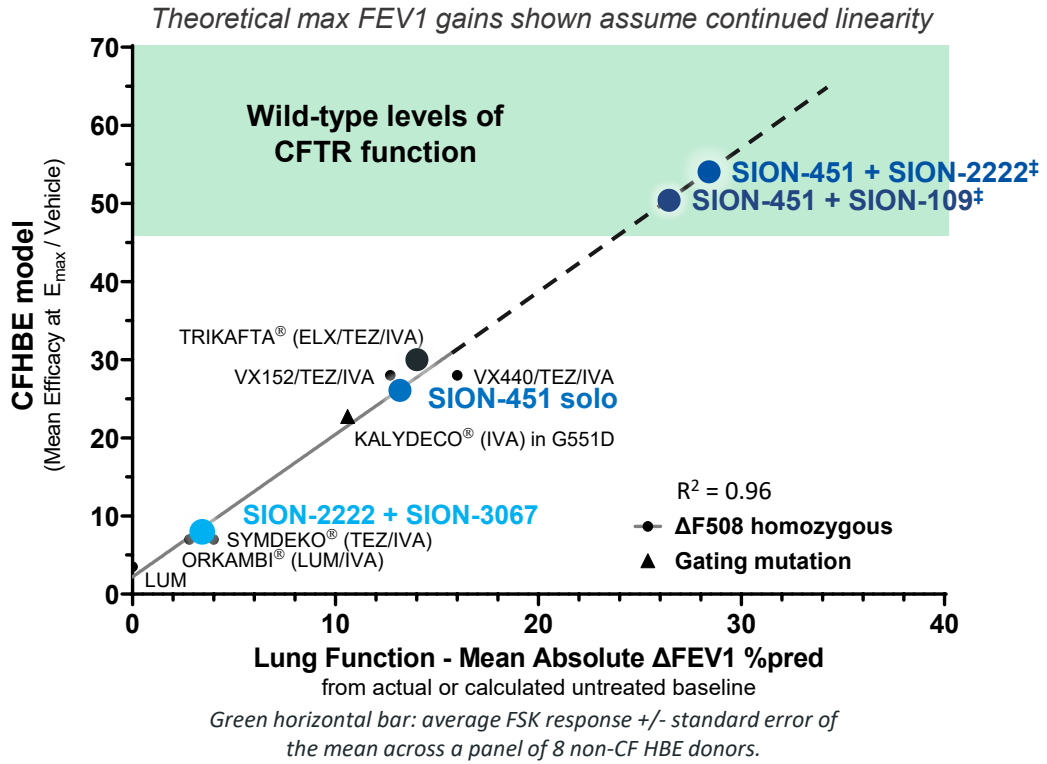
SION-451: Phase 1 ready NBD1 stabilizer demonstrates potential to normalize CFTR function as a dual combo

Potential of SION-451 at E_{max}



Green horizontal bar: average FSK response +/- standard error of the mean across a panel of 8 non-CF HBE donors.

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® at high SION-451 exposures
- Wild-type levels of CFTR function in double combination with a Sionna complementary CFTR modulator
- Wild-type levels of CFTR function as add-on to Trikafta®*+

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* Source: Pre-clinical assays conducted by Sionna; + Data not shown

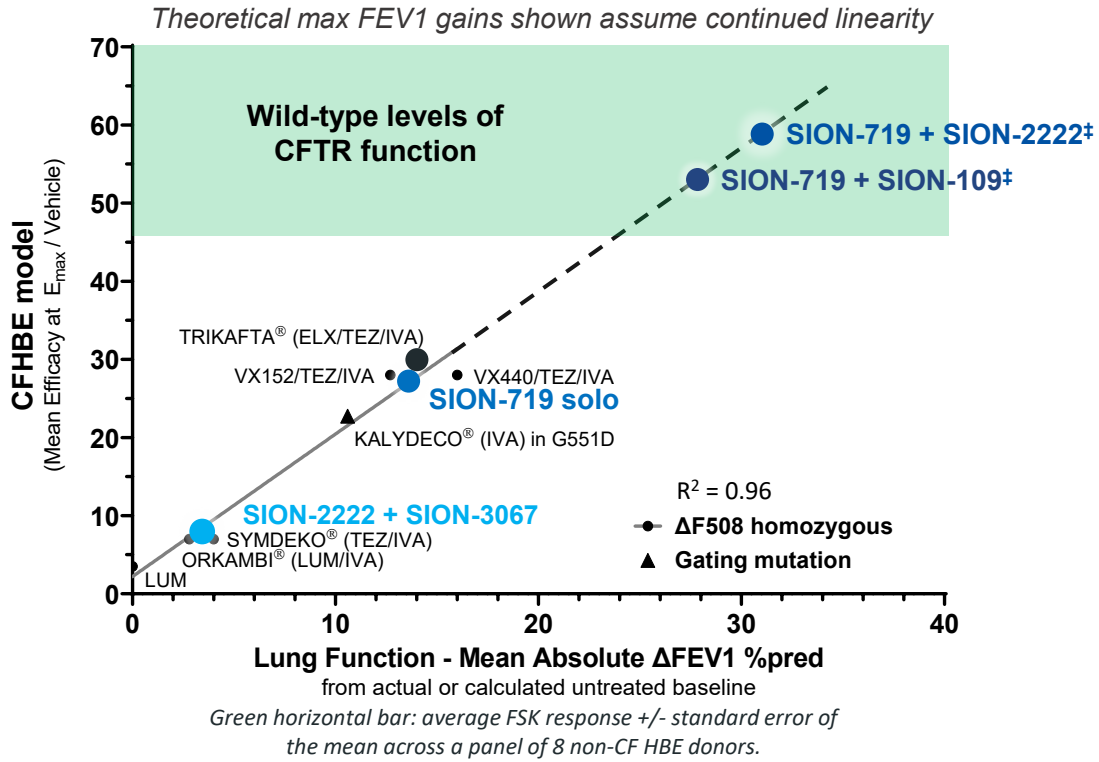
CFHBE - CF Human Bronchial Epithelial primary cells, DC - Development Candidate, FEV- Forced Expiratory Volume, Gating mutation - G551D CFTR, ELX - elexacaftor, IVA - ivacaftor, LUM - lumacaftor, SOC - Standard of Care, TEZ - tezacaftor, Trikafta - ELX/TEZ/IVA.

Trikafta®, Symdeko®, and Orkambi® are registered trademarks of Vertex Pharmaceuticals

‡ Mean CFHBE efficacy for SION-451+SION-2222 and SION-451+SION-109 are within the wild-type range at Emax. Across experiments, the difference in efficacy between these dual NBD1 combos is statistically non-significant

SION-719: Phase 1 ready NBD1 stabilizer provides another strong option to increase the CF efficacy bar

Potential of SION-719 at E_{max}



Green horizontal bar: average FSK response +/- standard error of the mean across a panel of 8 non-CF HBE donors.

Multiple options to raise the efficacy bar

In the clinically predictive CFHBE assay*, SION-719 has demonstrated the potential for:

- Single-agent efficacy equivalent to Trikafta® at high SION-719 exposures
- Wild-type levels of CFTR function in double combination with a Sionna complementary CFTR modulator
- Wild-type levels of CFTR function as add-on to Trikafta®*+

* Source: Pre-clinical assays conducted by Sionna; + Data not shown

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.

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‡ Mean CFHBE efficacy for SION-719+SION-2222 and SION-719+SION-109 are within the wild-type range at Emax. Across experiments, the difference in efficacy between these dual NBD1 combos is statistically non-significant

Lead Complementary Programs: Galicaftor (SION-2222) & SION-109

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TMD1 directed corrector galicaftor (SION-2222) is an attractive combination agent with NBD1 stabilizers

Mechanism of Action	• TMD1-directed CFTR corrector
Rationale and Enthusiasm for Advancement	• Galicaftor (SION-2222) synergizes with NBD1-directed correctors in CFHBE assay • Ph 2 demonstrates sweat chloride and ppFEV$_1$ outcomes in combination with navocaftor (SION-3067, potentiator) comparable to approved duals (Symdeko® and Orkambi®) • API acquired to supply late-stage development
Status	• Phase 2 studies completed by AbbVie*
Key Upcoming Milestones	• Combo MAD initiation with NBD1 stabilizer 2H25
Preferred Use Case & TTP	• Part of a Sionna proprietary double

* ClinicalTrials.gov (June 2023)

API - Active Pharmaceutical Ingredient, DC - Development Candidate, GLP - Good Laboratory Practice, ICL4 - Intracellular Loop 4 of CFTR, IND - Investigational New Drug, MOAs - Mechanisms of Action, tox - Toxicology studies.

In Ph 1/Ph 2 studies, galicaftor (SION-2222) was well-tolerated in healthy volunteers & CF patients, showed improvement in pulmonary function

Phase 1

Healthy Volunteers (n=82/single agent, n=143/combination)

Well-tolerated at all doses as single agent or combination with other modulators

- Up to 600 mg QD, 14d as single agent
- Up to 300 mg QD, 14d as combination

No significant PK DDI with any other modulators tested in combination

$t_{1/2}$ ~ **12hr**

Phase 1b

CF Patients (n=6/single agent)

100 mg single dose SION-2222 or PBO

Well-tolerated, PK similar to healthy volunteers

Phase 2

CF Patients (n = 48/single agent, n=125/ combination)

50-400 mg QD SION-2222 vs PBO, or 10-300 mg QD SION-2222/150 mg QD SION-3067 vs PBO in F/F CF patients for 4 weeks

200 mg QD **SION-2222 significantly decreased SwCl** as single agent therapy in F/F patients

200 mg QD **SION-2222 significantly improved pulmonary function, and decreased SwCl** as dual combination with SION-3067

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References: ClinicalTrials.gov (June 2023), ABBV-2222 Investigator Brochure (ed 5), 2022; Bell SC, Barry PJ, De Boeck K, et al. CFTR activity is enhanced by the novel corrector GLPG2222, given with and without ivacaftor in two randomized trials. J Cyst Fibros 2019;18:700–707.
Licensed compounds from AbbVie: galicaftor SION-2222 (FKA ABBV-2222) and navocaftor SION-3067 (FKA ABBV-3067)

SION-109, ICL4-directed modulator in Phase 1

Mechanism of Action	• ICL4-directed CFTR corrector
Rationale and Enthusiasm for Advancement	• SION-109 synergizes with NBD1-directed stabilizers • Promising potency and drug-like profile and tractable predicted target clinical dose • No adverse findings in 28-day GLP rat and dog tox, robust margins to target clinical exposures • API manufacture completed to support early clinical development
Status	• Phase 1 study initiated in 1Q24
Key Upcoming Milestones	• Completion of Phase 1 in 2H24
Preferred Use Case & TTP	• Part of a Sionna proprietary double combination

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API - Active Pharmaceutical Ingredient, DC - Development Candidate, GLP - Good Laboratory Practice, ICL4 - Intracellular Loop 4 of CFTR, IND - Investigational New Drug application, MOAs - Mechanisms of Action, tox - Toxicology studies.


Clinical and Portfolio Strategy
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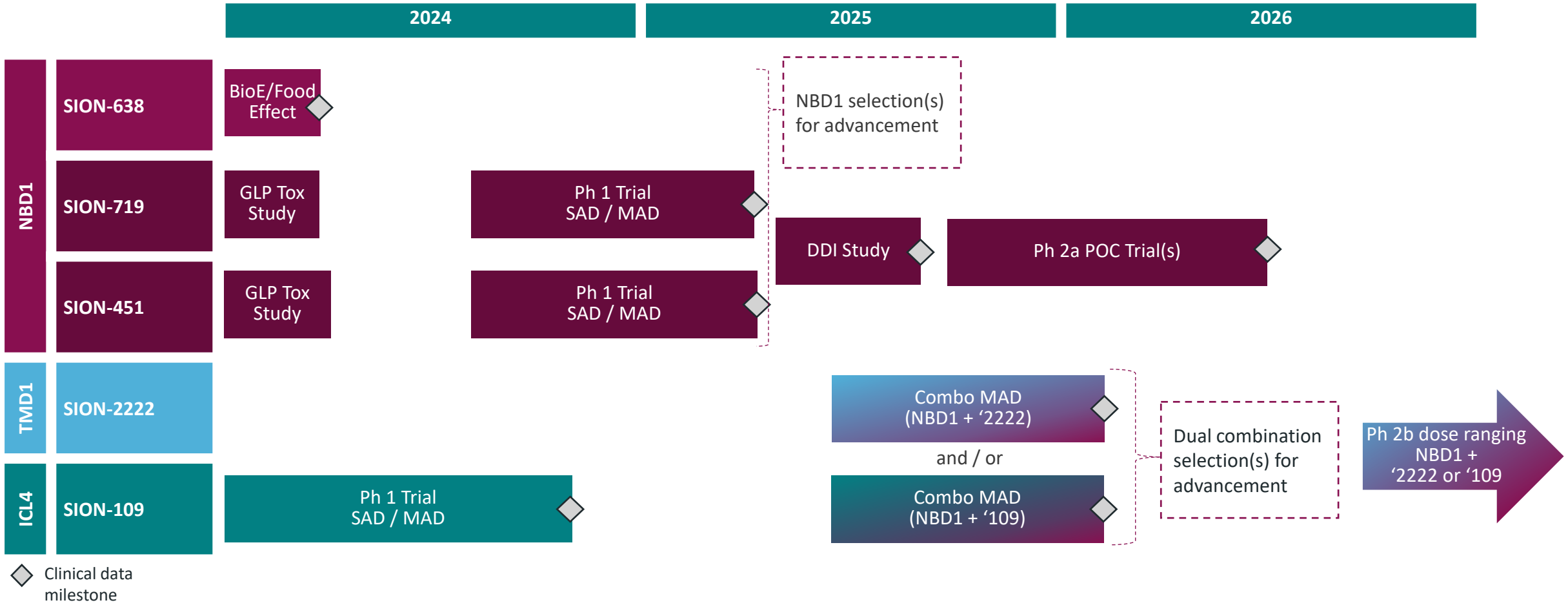
Sionna's dual combination path will be data driven, selecting the best NBD1 and complementary compounds from our deep pipeline



Unmet Need

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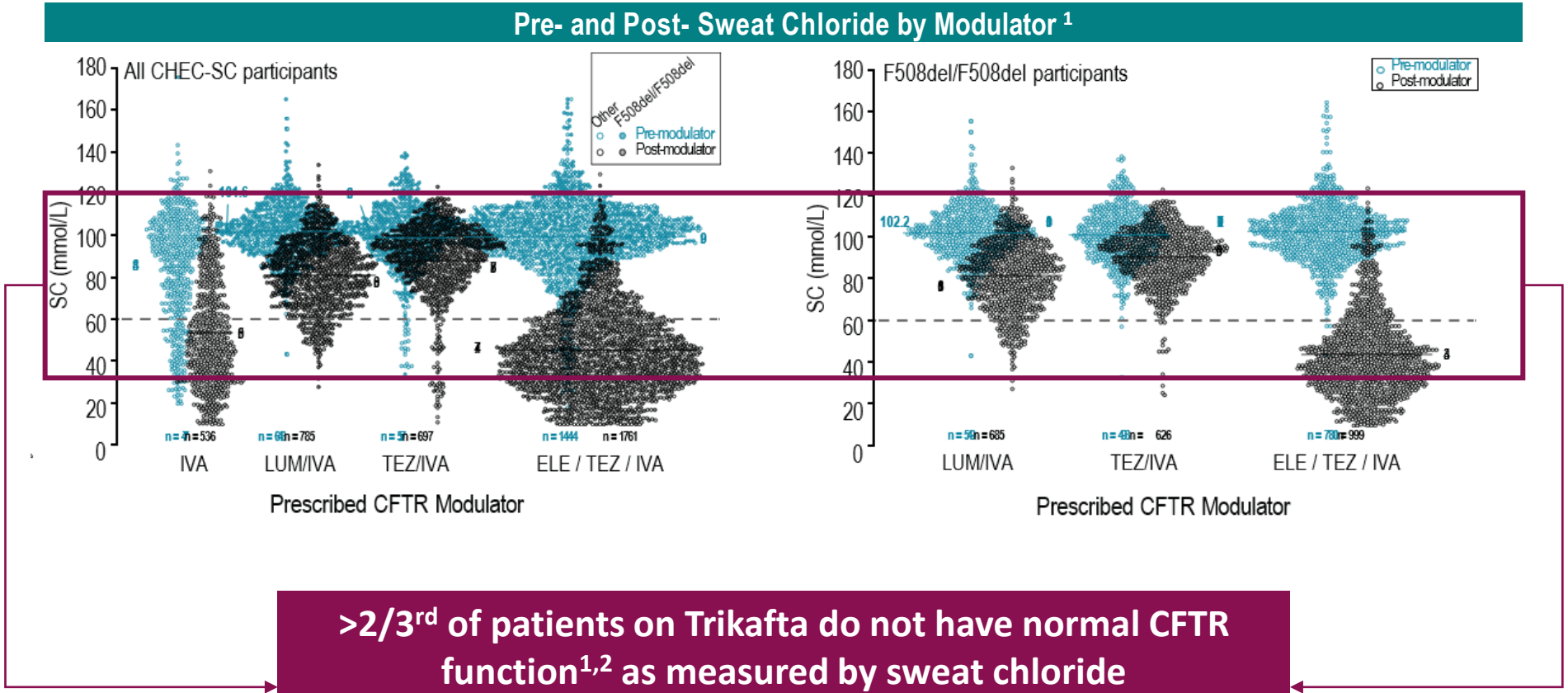
The efficacy unmet need remains high, as the goal is to achieve normal CFTR function for CF patients



>2/3rd of patients on Trikafta do not have normal CFTR function[1,2] as measured by sweat chloride

Normal sweat chloride = <30 mmol/L

Left panel, all CHEC-SC participants
- F508del/F508del are solid circles

Right panel, F508del/F508del participants
n = number of participants pre- (blue) and post- (black) modulator
Bold lines are pre- and post-modulator SC means
IVA = ivacaftor; LUM = lumacaftor; TEZ = tezacaftor; ELE = elexacaftor

1. Konstan, NACFC poster 2022
2. Zemanick, JCF 2024

Commitment to advancing game changing therapies, building significant near-term value, and raising the efficacy bar in CF

DELIVER

ROBUST NBD1 PORTFOLIO

- SION-638 Phase 1 completed in 1H24
- SION-719 Phase 1 initiation mid 2024
- SION-451 Phase 1 initiation mid 2024

ADVANCE

COMPLEMENTARY TARGETS

- Portfolio includes multiple clinical stage combo shots on goal:
  - Galicaftor (SION-2222), a TMD1 modulator with Ph 2 data in CF patients
  - SION-109 (ICL4 modulator), Phase 1 data 2H24
  - SION-2851 and SION-3067 create options for lifecycle development opportunities

BUILD

COMPANY CAPABILITIES

- Goal is to execute the strategy, grow the company, and build capabilities to become a leader in CF
- Cash runway through 2026 and Ph 2a POC