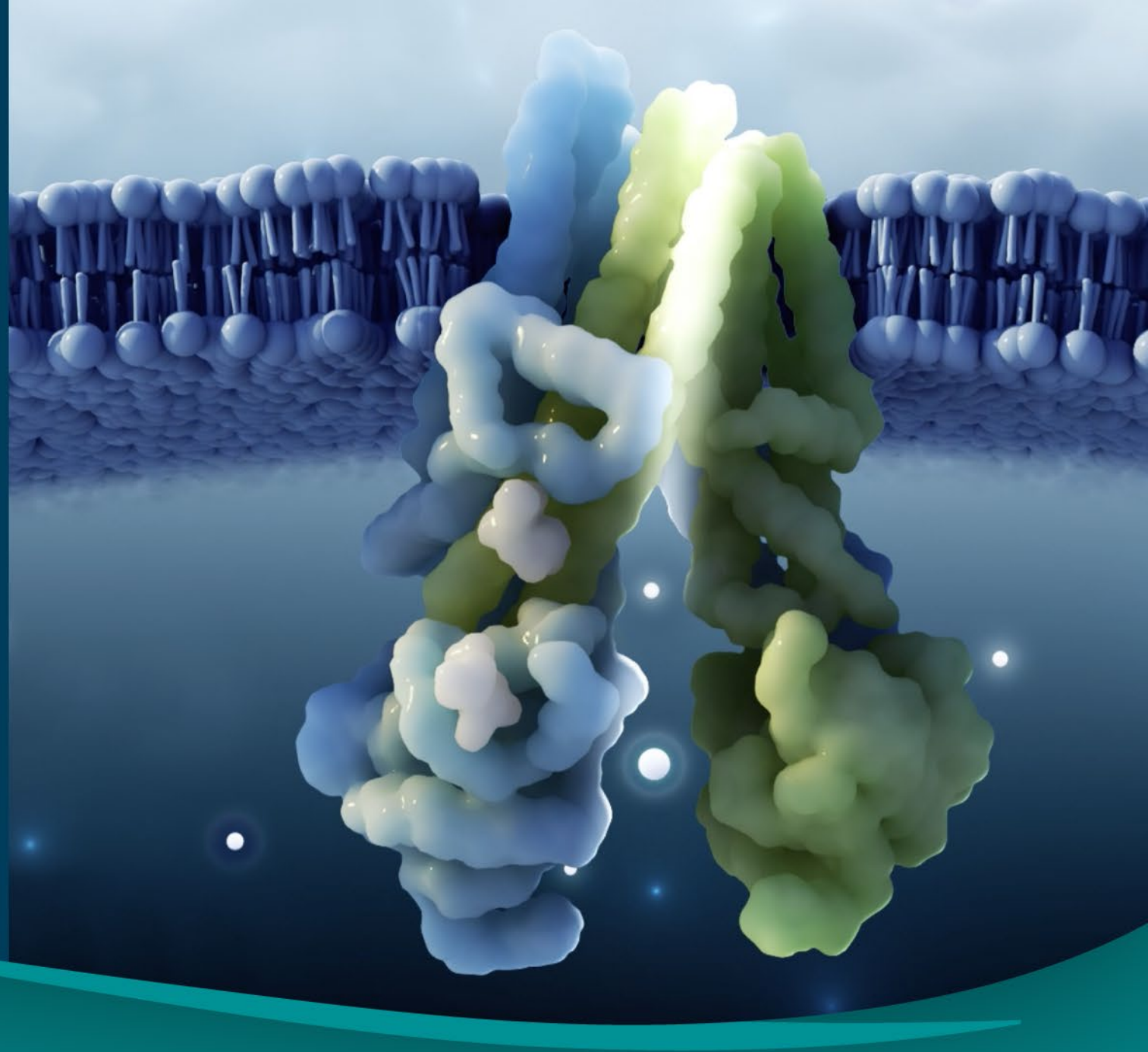
Sionna Therapeutics

On a Mission to Revolutionize the Cystic Fibrosis Treatment Paradigm

November 10th 2026



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Disclaimers and forward-looking statements

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The Sionna Opportunity
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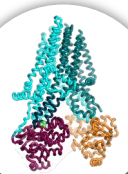
Sionna's novel approach focused on stabilizing NBD1 has the potential to revolutionize the current CF treatment paradigm

HIGH UNMET NEED IN LARGE MARKET

>2/3rd of patients on SOC do not have normal CFTR function

~$13B market today with a single-player

More options are needed



WE BELIEVE NBD1 IS CRITICAL

F508del resides in NBD1, the root defect in **~90%** of CF

No approved modulator directly stabilizes NBD1

Nonclinical data demonstrate **unique role of NBD1 stabilization**



SION-451 + SION-2222 ADVANCING TO Ph 2 POC

Two-drug combo designed to match or exceed CFTR function of today's triples

Favorable Ph 1 tolerability and PK in go-forward dose range

AscenSION CF POC expected to initiate **1Q27**

FOCUSED STRATEGY, CAPITAL TO DELIVER

~$250M cash as of 3Q26

Prioritized investment in **SION-451 + SION-2222**

Runway into 2H29, expected to fund AscenSION CF and beyond

NBD1 - Nucleotide Binding Domain 1 of CFTR (CF transmembrane conductance regulator); CF – Cystic Fibrosis; Ph – Phase; POC – proof-of-concept; SwCl – sweat chloride; SOC – standard of care
Post hoc analyses are exploratory and may not reliably predict future outcomes

Proven leadership with deep CF and drug development experience

Leadership



Mike Cloonan

Chief Executive Officer

Sage Therapeutics, Biogen, Bain & Company



Charlotte McKee, M.D.

Chief Medical Officer & Head of R&D

Vertex, Infinity Pharmaceuticals, TOLERX, Wyeth, Brigham and Women's Hospital



Elena Ridloff, C.F.A.

Chief Financial Officer & Chief Business Officer

Acadia, Alexion



Jen Fitzpatrick

Chief Legal Officer & Head of Program Management

Sage Therapeutics, Aegerion Pharmaceuticals, AVEO Oncology



Mark Trone

SVP, Head of Technical Operations

Blueprint Medicines a sanofi company, Alkermes, GSK, Takeda

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CMO, Tectonic Therapeutic

Peter Thompson, M.D.
Partner, Orbimed

Jo Viney, Ph.D.
CEO, Seismic Therapeutic

Sionna is built on more than 15 years of pioneering NBD1 research

2009

Foundational NBD1 and CFTR research begins in stealth at Genzyme and Sanofi

2019

CF program spun out of Sanofi, supported by CFF

2022

Sionna emerged from stealth with $150M in funding

2024

$182M Series C; two NBD1 Ph 1 trials initiated; in-licensed AbbVie CF assets to expand pipeline

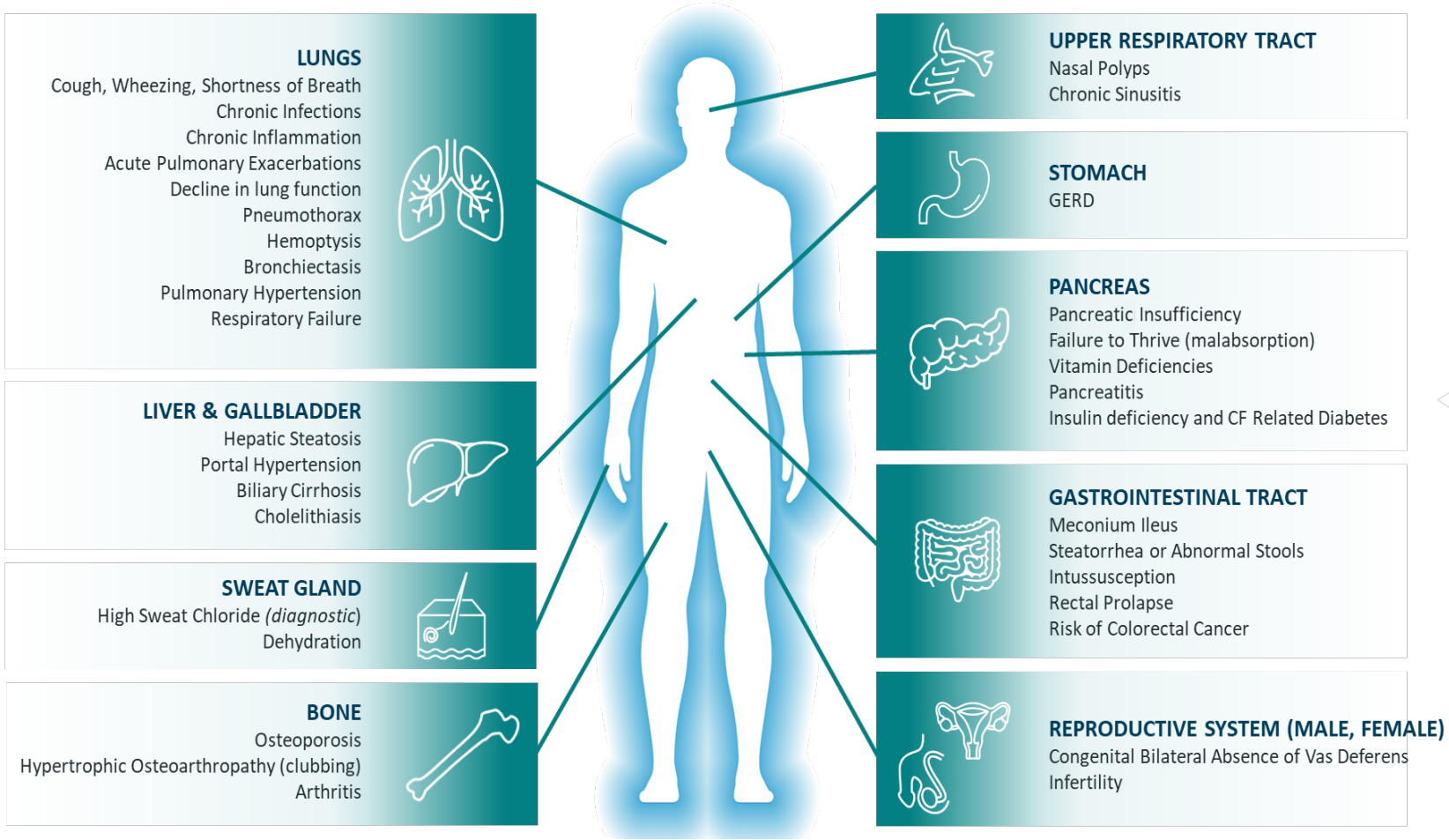
2025

$219M IPO; positive Ph 1 data for two NBD1 stabilizers

2026

SION-451 + SION-2222 advancing to POC, based on positive Ph 1 readout and PreciSION CF learnings

CF is a rare, progressive and life-threatening genetic disease with debilitating multi-system complications



Progress made, but more to do

~106K

people affected with CF globally[1]

65 years

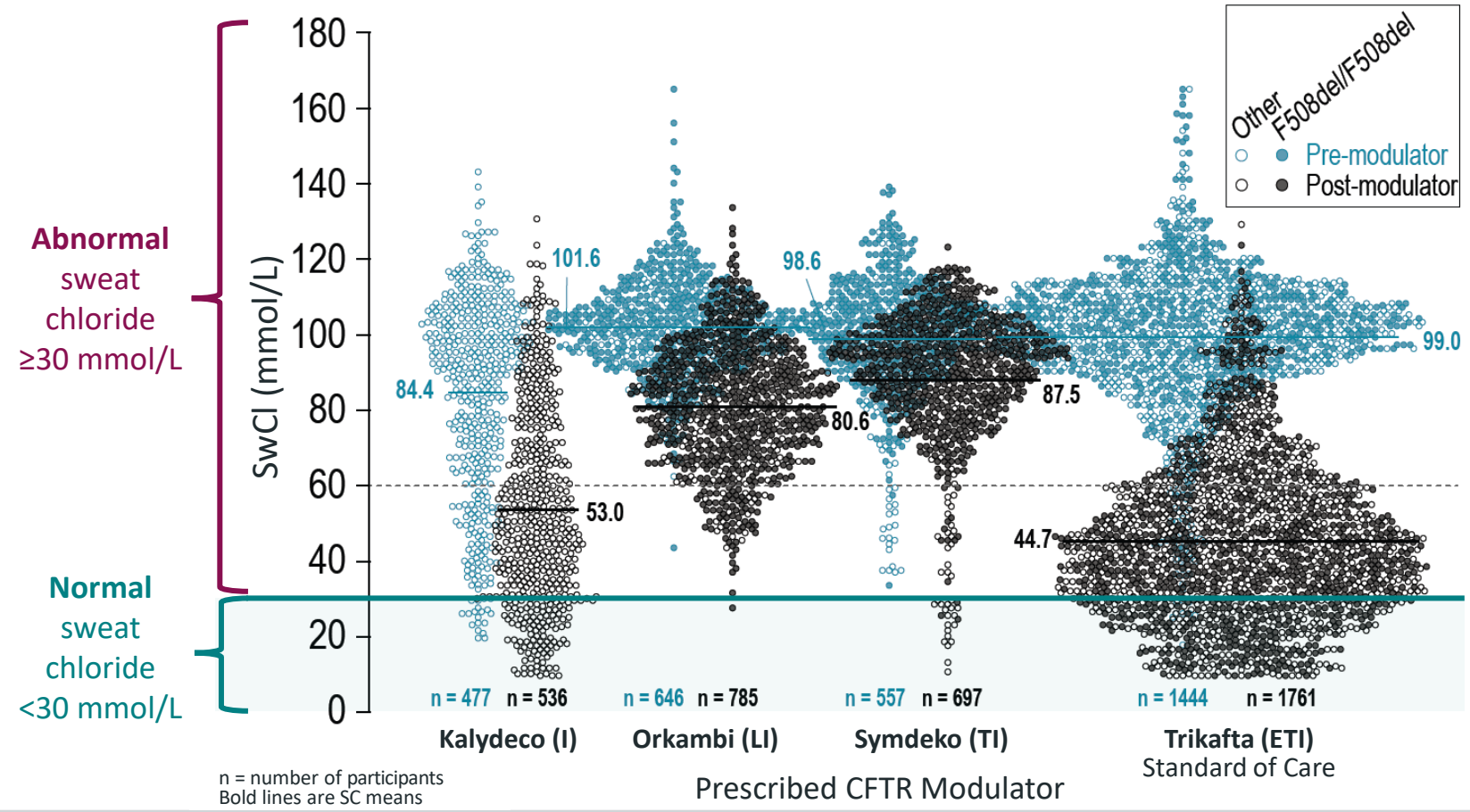
predicted median survival for people with CF born in the U.S. in 2020–2024[2]

Further advances are needed so more people with CF can live longer, healthier lives

1. CFF estimates 2024, 2024 CFF Registry data, 2022 ECFS Registry; 2. 2024 CFF Patient Registry Annual Data Report

Despite advancements in treatment, the unmet need remains high, as many CF patients on treatment do not achieve normal CFTR function

CHEC-SC Study; All Patients Pre- and Post- Modulator[1*]



n = number of participants
Bold lines are SC means

>2/3rd

of patients on Trikafta do not have normal CFTR function[1,2]

as measured by sweat chloride <30 mmol/L

~69% of Alyftrek patients in two Phase 3 clinical trials conducted by Vertex **did not achieve normal CFTR function[3]**

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1. Konstan, NACFC poster 2022; 2. Zemanick, JCF 2024;
3. Vertex press release, Feb 5th 2024;
** Observational study of 3,131 CF patients from the CFF Registry showing sweat chloride levels pre- and post- treatment of a CFTR modulator*

NBD1 is a critical CF target and a differentiated approach to restoring F508del-CFTR function

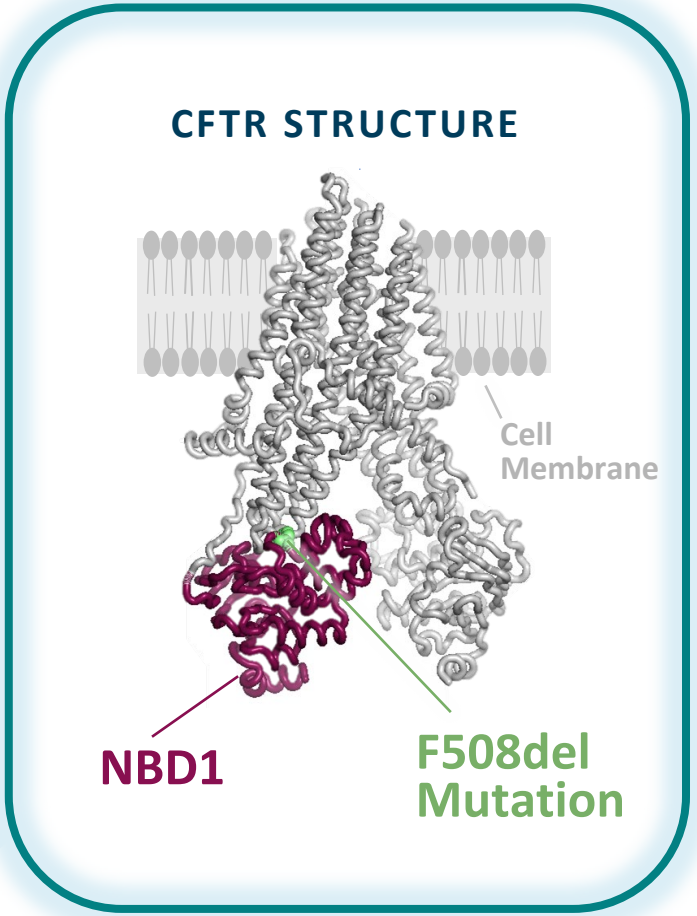
Cystic Fibrosis and NBD1 Biology

~90% of people with CF carry F508del[1], **which resides within NBD1**[2]

F508del destabilizes NBD1, impairing CFTR folding, trafficking and function[2,3]

We believe **NBD1 stabilization is critical** to achieving normal CFTR function[3]

No approved CFTR modulator directly stabilizes NBD1



1. Taylor-Cousar 2019; 2. Thibodeau 2010; 3. Rabeh 2019; He 2014

Meaningful opportunity exists for alternative CF treatment options beyond the standard of care

HIGH UNMET NEED

CFTR Function

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

Tolerability Challenges

Many on SOC experience tolerability challenges, including **liver side effects** and **CNS burden**[3]

Limited Options for Patients

Alyftrek showed **noninferior lung function** vs. Trikafta[4]; All approved triple combination drugs have the same MOAs

GROWING MARKET

~$13B
market today[5]

~$15–17B
expected by 2030[6]

SIONNA'S APPROACH

SION-451 NBD1 | **SION-2222** TMD1

An investigational dual combination designed to directly stabilize NBD1

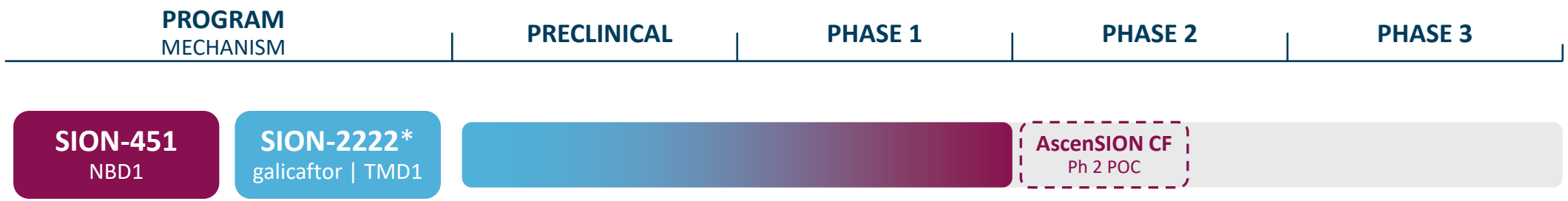
A two-drug regimen to be evaluated in the AscenSION CF Ph 2 POC trial, expected to initiate 1Q27

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1. Konstan, NACFC poster 2022; 2. Zemanick, JCF 2024 (normal sweat chloride <30 mmol/L);
3. Trikafta USPI (March 2026); Alyftrek USPI (March 2026); 4. Keating, Lancet 2025;
5. VRTX 3Q26 earnings call; 6. Wall Street research estimates
CNS – central nervous system; MOA – mechanism of action

Sionna's pipeline is focused on advancing our proprietary dual combination, SION-451 + SION-2222

SIONNA'S PROPRIETARY DUAL COMBINATION



Phase 1 dual combination trial in healthy participants completed; Phase 2 proof-of-concept trial expected to initiate 1Q27

ADDITIONAL CLINICAL ASSETS IN SIONNA'S PIPELINE

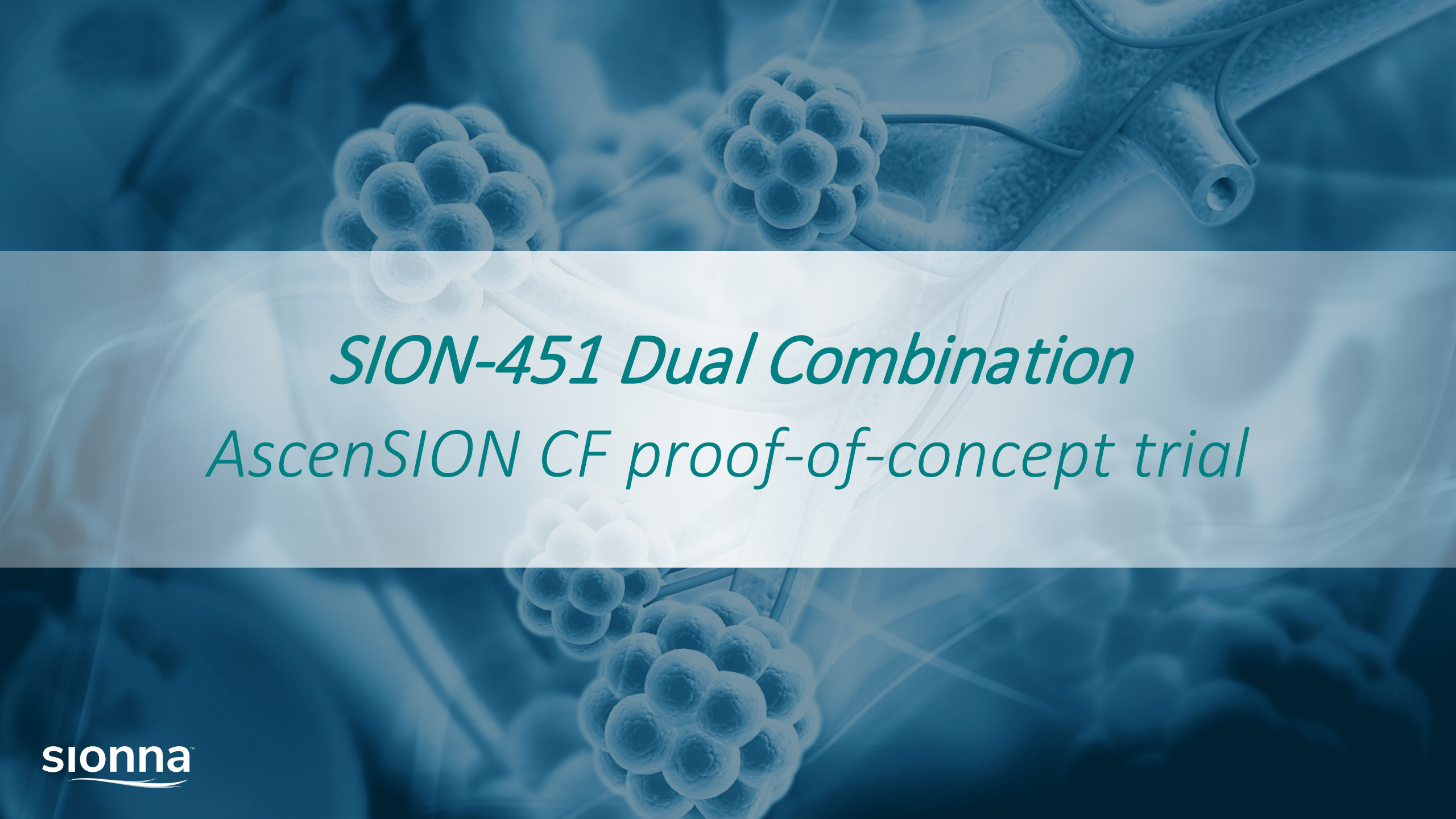
NBD1 STABILIZER

- **SION-719** — NBD1

COMPLEMENTARY MODULATORS

- **SION-109** — ICL4
- **SION-2851** — TMD1
- **SION-3067*** — Navocaftor | TMD2 (potentiator)

*Licensed from AbbVie; galicaftor and navocaftor completed Ph 2 combination trials conducted by AbbVie
TMD – transmembrane domain 1 and 2 of CFTR; ICL4 – intracellular loop 4 of CFTR



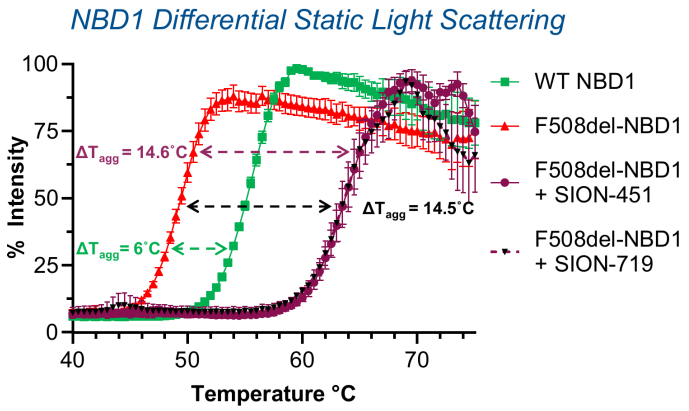
SION-451 Dual Combination

AscenSION CF proof-of-concept trial

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Nonclinical data demonstrate unique role of NBD1 stabilization to correct multiple dimensions of F508del-CFTR dysfunction

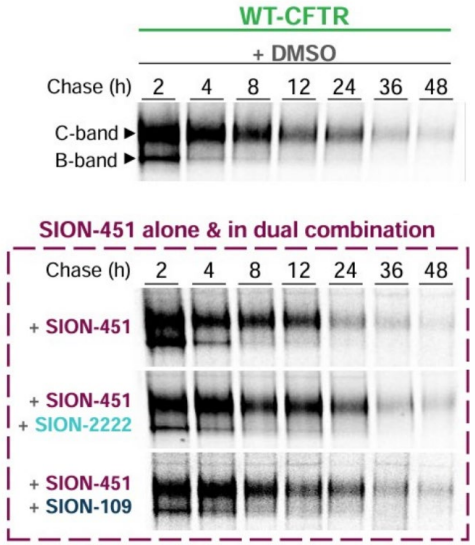
1 NBD1 Thermal Stability



NBD1 compounds stabilize the unstable NBD1 region

SION-451 raised the temperature at which F508del-NBD1 unfolds by ~15°C, up to normal temperature levels

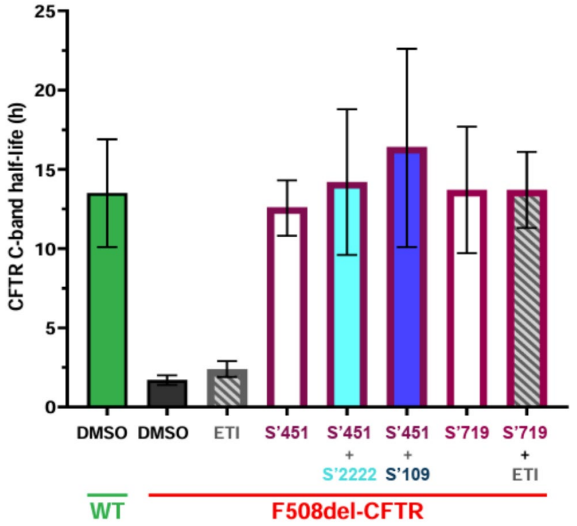
2 Protein Maturation



Stabilizing NBD1 leads to more mature CFTR protein

At E_{max}, SION-451 + SION-2222 increased mature F508del-CFTR up to wild-type levels

3 Protein Half-Life



NBD1 improves half-life of the protein up to wild-type levels

At E_{max}, SION-451 +SION-2222 improved half-life up to 14.2h vs. 1.7h untreated and 2.4h with ETI; this is comparable to wild-type

Nonclinical studies conducted by Sionna; results observed in preclinical models may not be predictive of clinical outcomes
DSLS – differential static light scattering; ETI – elexacaftor/tezacaftor/ivacaftor, the components of Trikafta; WT – wild-type

Phase 1 established SION-451 + SION-2222 as our dual combination

Design	Results	Decision
Safety, tolerability, and PK evaluated across **multiple dose combinations** in healthy volunteers SION-451 NBD1 + SION-2222 TMD1 SION-451 NBD1 + SION-109 ICL4	**Achieved safety and tolerability objectives**	**SION-451 BID + SION-2222 QD selected** as dual combination based on target coverage SION-451 NBD1 + SION-2222 TMD1
3:1 randomized, double-blind, placebo-controlled All cohorts dosed for 14 days	**Exceeded PK target** in go-forward dose range	Advancing to AscenSION CF Ph 2 POC, expected to initiate 1Q27
Per combination, 60 participants dosed across 5 cohorts	**Combination PK consistent** with respective single-agent Phase 1 profiles	SION-109 remains an additional pipeline asset

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PK – pharmacokinetics; BID – twice daily; QD – once daily

SION-451 BID + SION-2222 QD demonstrated a favorable tolerability profile

	Placebo	SION-451 BID + SION-2222 QD	SION-451 BID + SION-2222 BID	Total
Trial Participants (n)	*(n=15)*	*3 cohorts (n=27)*	*2 cohorts (n=18)*	*(n=60)*
Participants with any TEAE, n (%)	**5 (33)**	**19 (70)**	**10 (56)**	**34 (57)**
Mild (Grade 1)	5 (33)	15 (56)	10 (56)	30 (50)
Moderate (Grade 2)	1 (7)	10 (37)	5 (28)	16 (27)
Severe (Grade 3)[1]	-	-	2 (11)	2 (3)
Leading to treatment discontinuation	-	1 (4)	2 (11)	3 (5)
Serious TEAEs, n (%)	**-**	**-**	**-**	**-**
Most frequent TEAEs (≥3 participants), n (%)				
Headache	4 (27)	4 (15)	3 (17)	11 (18)
Diarrhea	1 (7)	6 (22)	4 (22)	11 (18)
Fever	-	-	4 (22)	4 (7)
Abdominal Pain	-	2 (7)	1 (6)	3 (5)
Elevated Liver Associated Enzymes[2]	-	-	3 (17)	3 (5)
Intravenous Site Phlebitis	-	2 (7)	1 (6)	3 (5)

SION-451 BID + SION-2222 QD
preferred regimen

All cohorts generally well tolerated

All TEAEs were mild to moderate with no SAEs and no TEAEs associated with elevated LFTs

Safety profile consistent with prior single agent clinical trials of SION-451 BID and SION-2222 QD

One participant discontinued due to moderate rash

SION-451 BID + SION-2222 BID

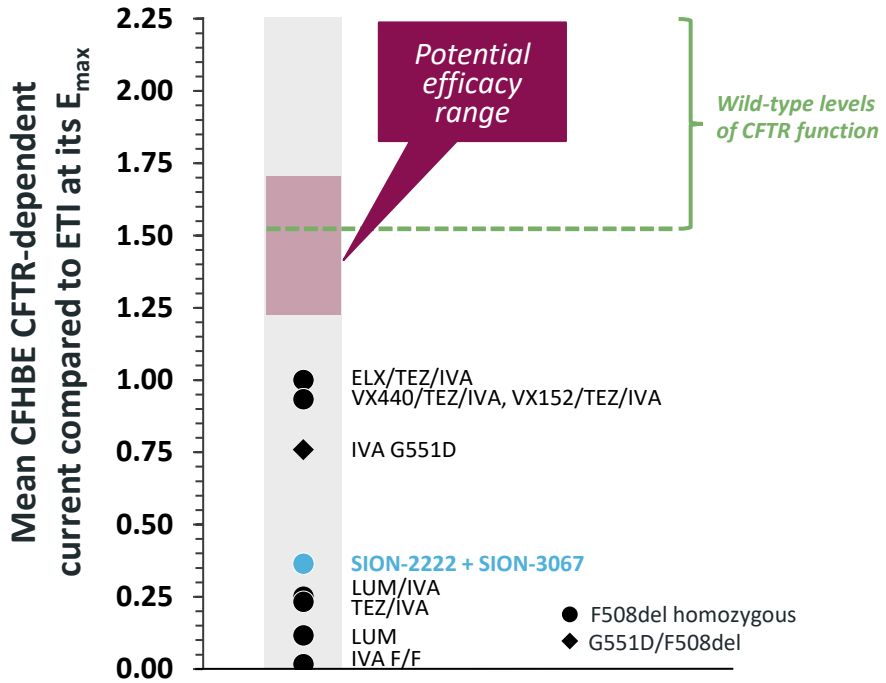
Most TEAEs were mild to moderate with no SAEs

Two participants discontinued due to elevated LFTs and flu-like symptoms; both cases were confounded[3]

TEAEs – treatment emergent adverse events (AEs); SAE – serious AE; LFT – liver function test
1. Grade 3 TEAEs of ALT increased, AST increased, GGT increased, lymphocyte count decreased, neutrophil count decreased
2. Elevated liver associated enzymes included alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase
3. Two participants dosed with SION-2222 BID who discontinued were confounded by other factors, including potential infection

CFHBE data demonstrate potential for SION-451 + SION-2222

CFHBE assay data of SION-451 + SION-2222 go-forward doses based on Ph 1 PK



Wild-type range is the average FSK response +/- standard error of the mean across a panel of 8 non-CFHBE primary cell donors

Assay Predictions

CFHBE assay shows the potential **efficacy range at observed Phase 1 PK** of the go-forward dose range

These exposures **predict CFTR benefit up to wild-type levels**

Clinical Proof-of-Concept

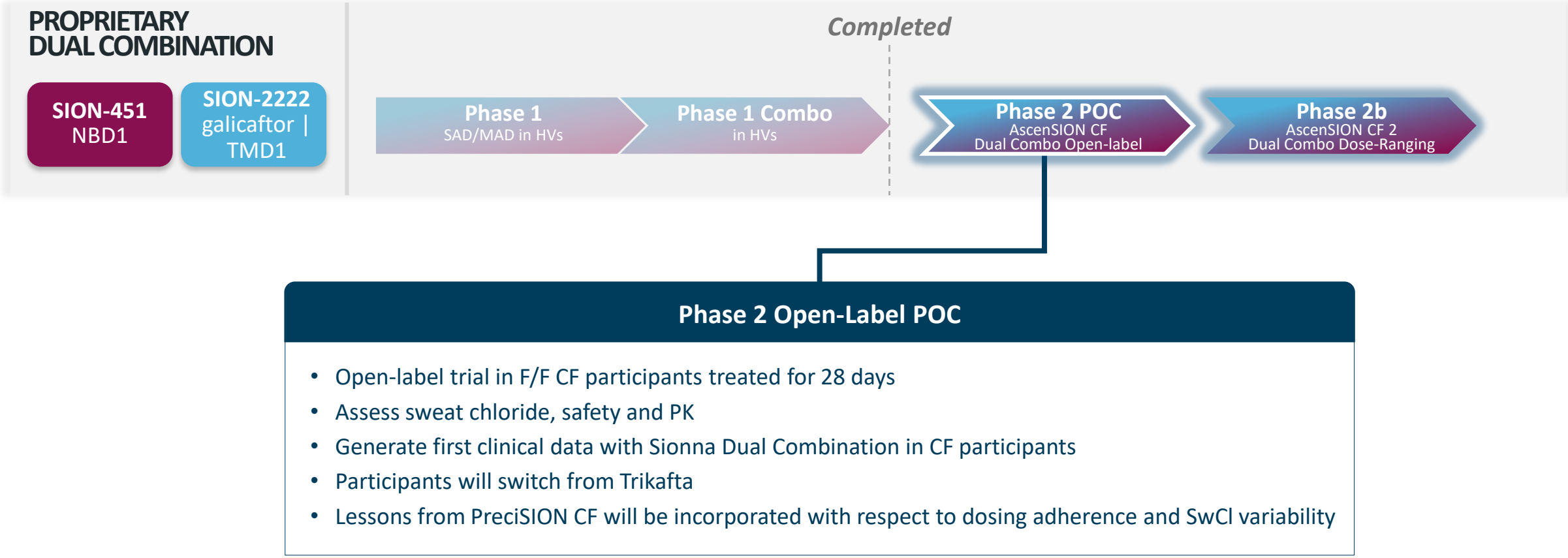
AscenSION CF will assess sweat chloride of SION-451 + SION-2222 in people with F/F CF

Superiority to SOC remains the goal; equivalent CFTR function would also be clinically meaningful

Source: nonclinical assays conducted by Sionna and based on Phase 1 PK; results observed from our nonclinical studies may not necessarily be predictive of clinical outcomes, and actual outcomes may differ

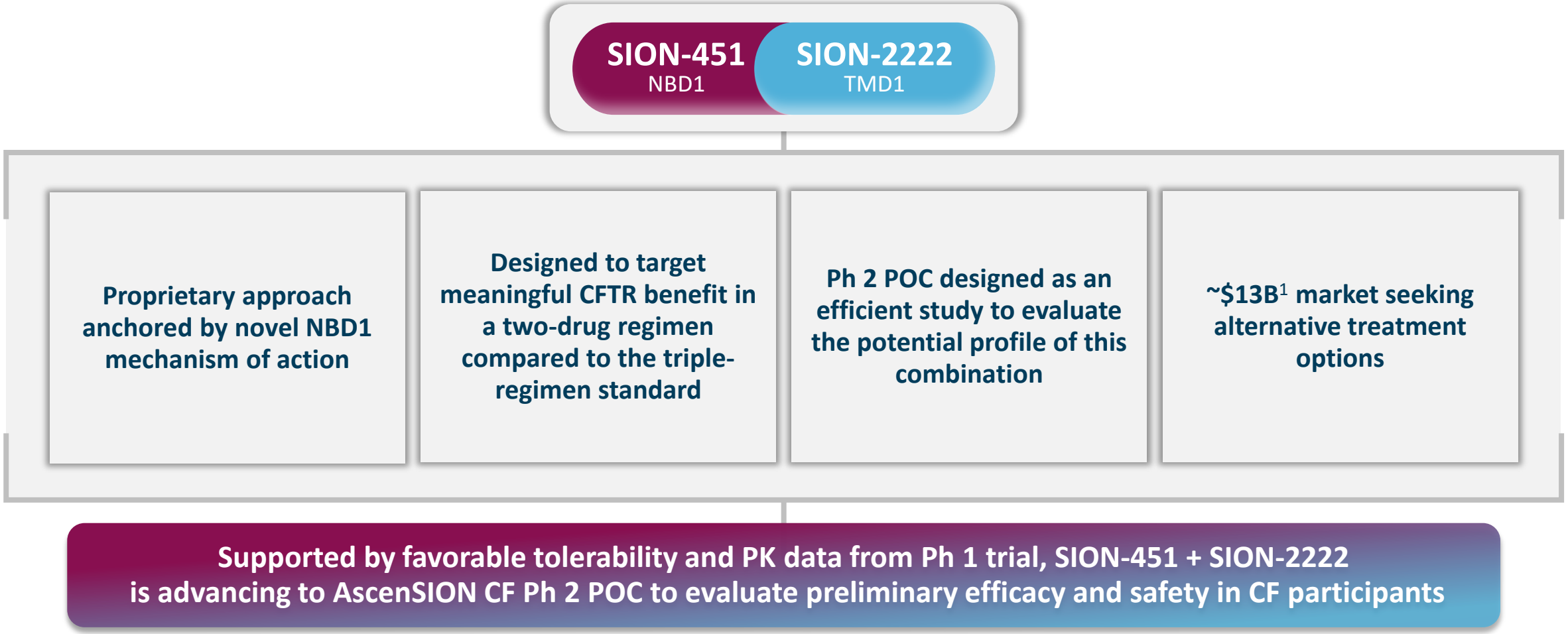
CFHBE – CF human bronchial epithelial cells; Gating mutation – G551D CFTR; ELX – elexacaftor; IVA – ivacaftor; LUM – lumacaftor; TEZ – tezacaftor; Trikafta – ELX/TEZ/IVA; F/F – homozygous for F508del mutation

AscenSION CF proof-of-concept trial of SION-451 + SION-2222 expected to initiate in 1Q27



SAD – single ascending dose; MAD – multiple ascending dose; HV – healthy volunteer

SION-451 + SION-2222 designed to offer a differentiated two-drug approach to current triple-combination standard of care therapies



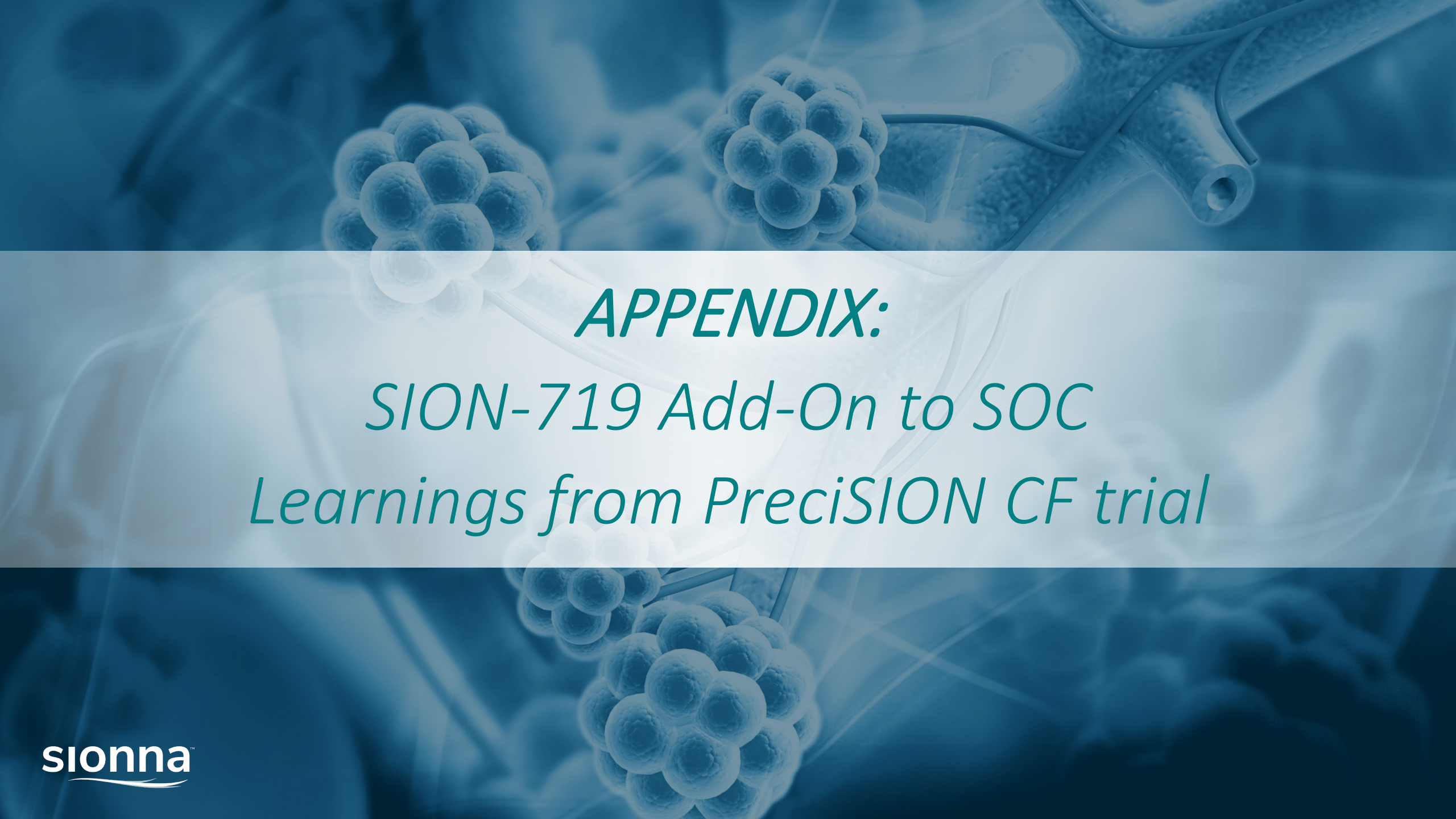
1. VRTX 3Q26 earnings call

Closing

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Focused execution of SION-451 + SION-2222 is the next step toward realizing the potential of NBD1 stabilization

NBD1 BIOLOGY REINFORCED	PreciSION CF post hoc analyses and nonclinical data support potential of NBD1 and advancement of SION-451 + SION-2222
DUAL COMBO OFFERS UNIQUE ADVANTAGE	SION-451 + SION-2222 is a potentially differentiated two-drug alternative in a market that desires new options
EFFICIENT PHASE 2 STRATEGY	AscenSION CF is an open-label proof-of-concept Ph 2 trial that incorporates learnings from PreciSION CF, expected to initiate in 1Q27
STRATEGIC CAPITAL RESOURCING	Cash runway into 2H29 that prioritizes investment in SION-451 + SION-2222



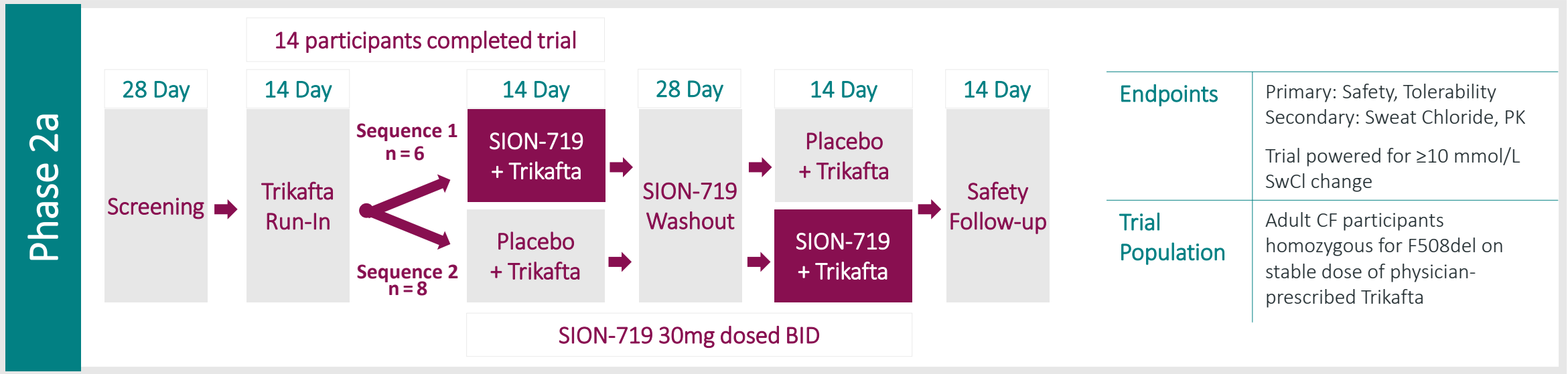
APPENDIX:

SION-719 Add-On to SOC

Learnings from PreciSION CF trial

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PreciSION CF Phase 2a trial used a randomized, double-blind crossover design to evaluate SION-719 added to background Trikafta



Endpoints	Primary: Safety, Tolerability Secondary: Sweat Chloride, PK Trial powered for ≥10 mmol/L SwCl change
Trial Population	Adult CF participants homozygous for F508del on stable dose of physician-prescribed Trikafta

Primary Analysis

Mean SwCl change from baseline at Day 1, during SION-719 and placebo treatment periods using MMRM

Secondary Analysis

Prespecified analysis of mean SwCl change from each treatment period baseline, during SION-719 and placebo periods using MMRM

MMRM – Mixed Model with Repeated Measures

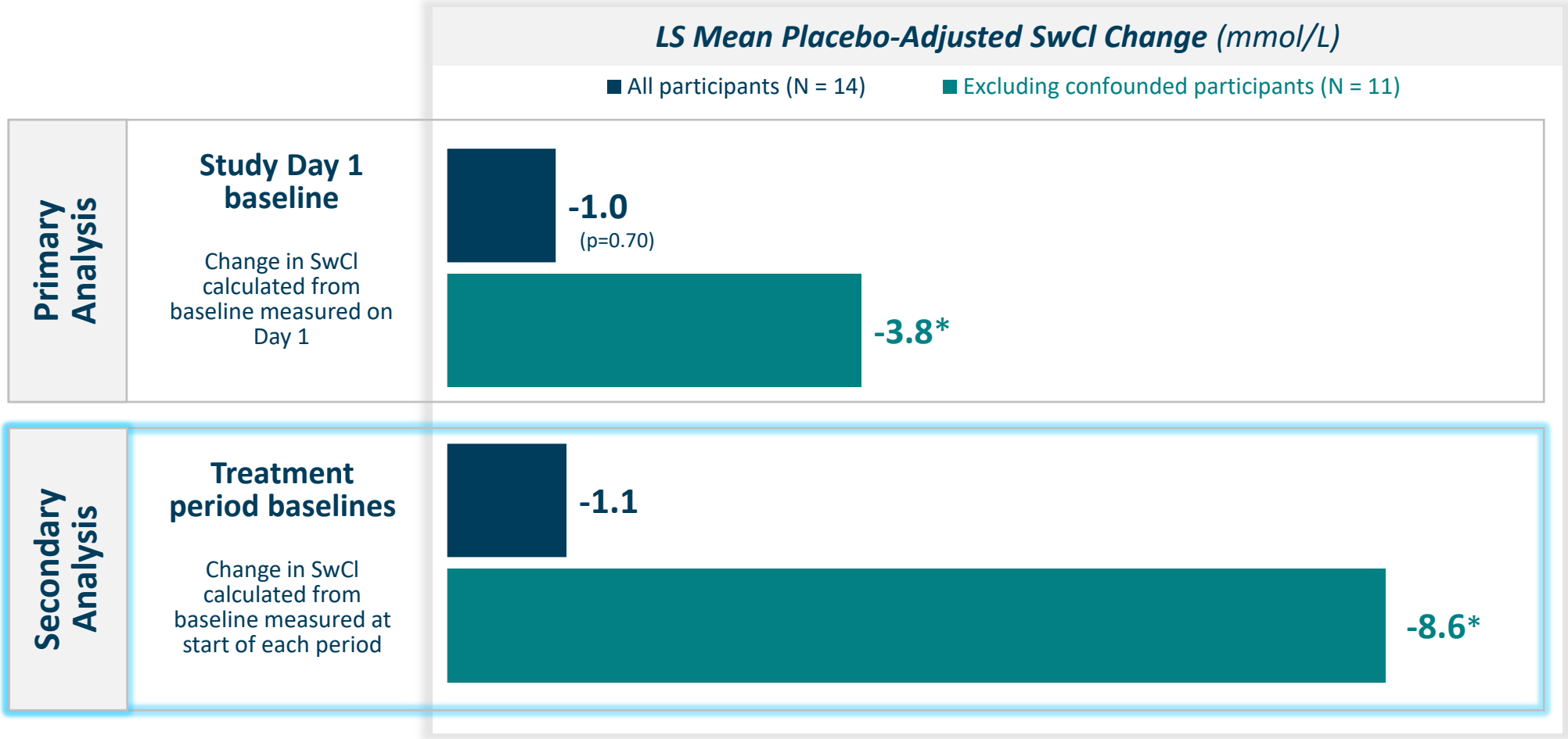
PreciSION CF topline data: SION-719 added to Trikafta was well tolerated but did not meet the key activity endpoint

Key Activity Endpoint	Mean placebo-adjusted sweat chloride change of **–1.0 mmol/L (p = 0.7)** with SION-719 30 mg BID added to Trikafta
Safety & Tolerability	SION-719 was generally well tolerated when added to Trikafta for 14 days; no meaningful trends in AEs
PK Exposure	SION-719 exposure in the study was consistent with single agent PK

SION-719 is not advancing as an add-on to SOC

Post hoc analysis identified three potential confounding factors, reviewed on the following slides

Post hoc analysis shows up to -8.6 mmol/L mean sweat chloride change, which we believe is evidence of NBD1 activity



*Post hoc analysis

PreciSION CF post hoc analysis identified three key potential confounding factors

1 PK Outliers

Three participants had no or unusually low SION-719 or Trikafta exposures, consistent with dosing non-adherence

Excluding these participants, signals of NBD1 target engagement and biological activity were observed

2 ETI Exposure

ETI exposures were lower by an average of ~25-30% during SION-719 treatment

Lower ETI exposures may have blunted incremental impact of NBD1

3 CFTR Channel Biology

SION-719 + ETI showed high CFTR current before stimulation in nonclinical assay

Four-drug combination potentially limited response by dysregulating the CFTR channel

ETI – elexacaftor/tezacaftor/ivacaftor, the components of Trikafta

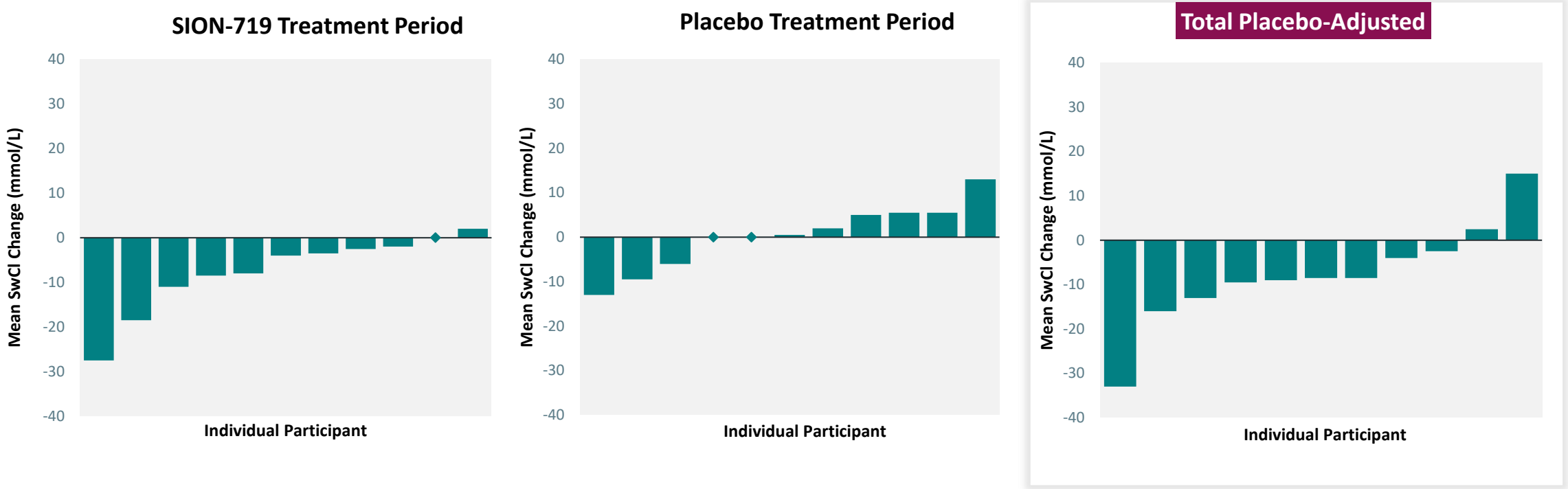
Removing 3 confounded participants, individual SwCl data are consistent with NBD1 activity

1 PK outliers

3 participants had no or unusually low SION-719 or Trikafta exposures, consistent with dosing non-adherence

Excluding these participants, signals of NBD1 target engagement and biological activity were observed

Secondary SwCl analysis - excluding 3 confounders (N=11)



Note: End of placebo-period values were imputed for two participants with missing observations. Participants are ordered within each panel by magnitude of sweat chloride change.

Individual SwCl changes calculated from each treatment period baseline

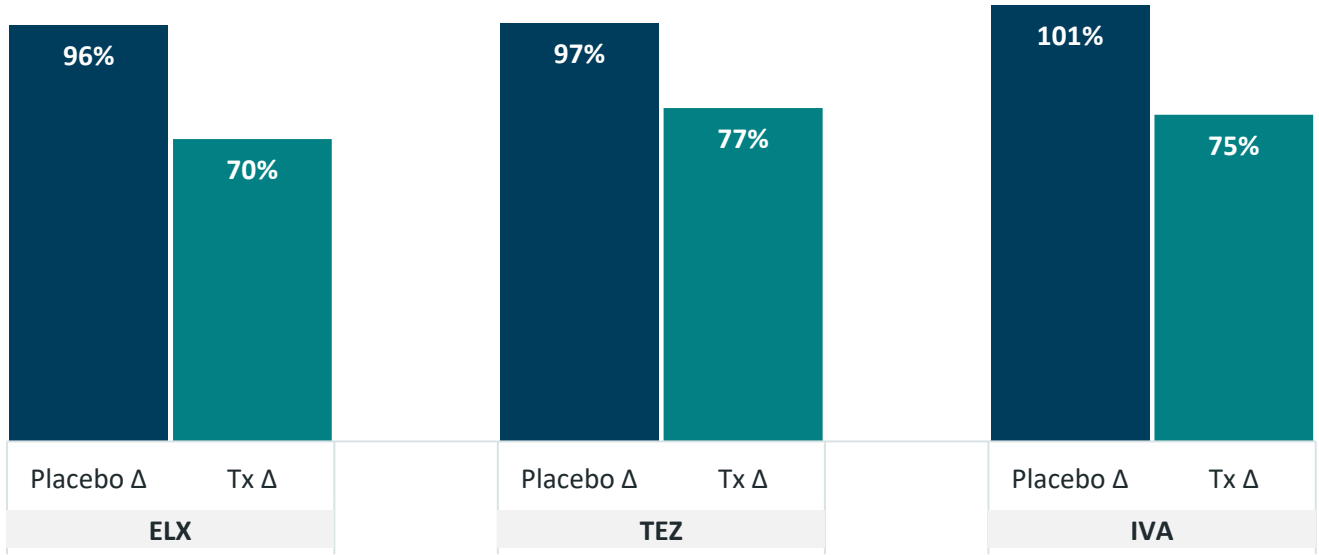
Trikafta exposures were lower during SION-719 treatment, which may have blunted the NBD1 effect

2 ETI exposure

ETI exposures were ~25–30% lower on average during SION-719 treatment

Lower ETI exposures may have blunted the incremental impact of NBD1

Change in mean concentrations of Trikafta (ETI) during placebo and treatment periods
Excluding 3 confounded participants (N=11)



Key observations

On average, decreased ETI exposures during SION-719 treatment

- ETI exposures were relatively stable during placebo periods but declined during SION-719 treatment
- We could not quantify the potential impact of this 4-drug interaction, but it is possible that lower Trikafta exposure may have blunted NBD1 impact
- We believe this confounding effect will not be a factor with our dual combination

Note: concentrations are trough (pre-dose) levels
ELX – elexacaftor; TEZ – tezacaftor; IVA – ivacaftor
Tx = treatment period

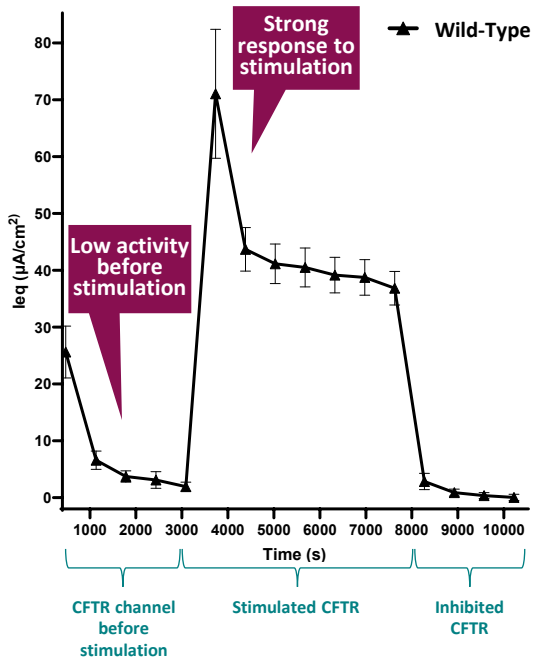
CFTR channel activity in CFHBE model supports the dual combination and highlights potential dysregulation with SION-719 + ETI

3 CFTR channel biology

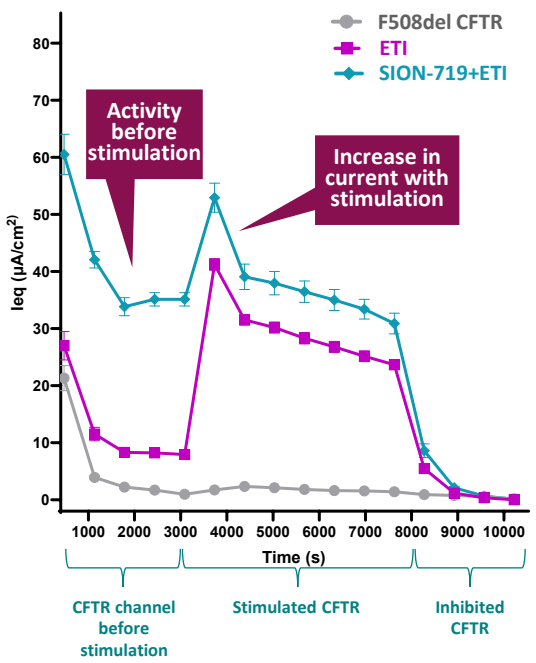
SION-719 + ETI showed high CFTR current before stimulation in a nonclinical assay

The four-drug combination may have limited response by dysregulating the CFTR channel

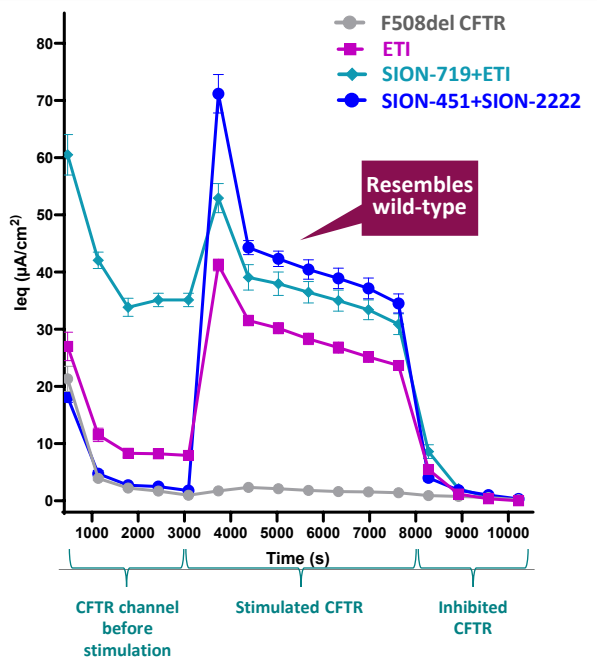
Normal regulation (wild-type)



SION-719 + ETI (add-on) at E_{max}



SION-451 + SION-2222 (dual combo) at E_{max}



Note: F508del-CFTR and wild-type traces shown each represent a single donor with 4 replicates, and are representative of the observed profiles from 6 donors in the same experiment

30mg of '719 pre stimulated current is ~50% of E_{max}