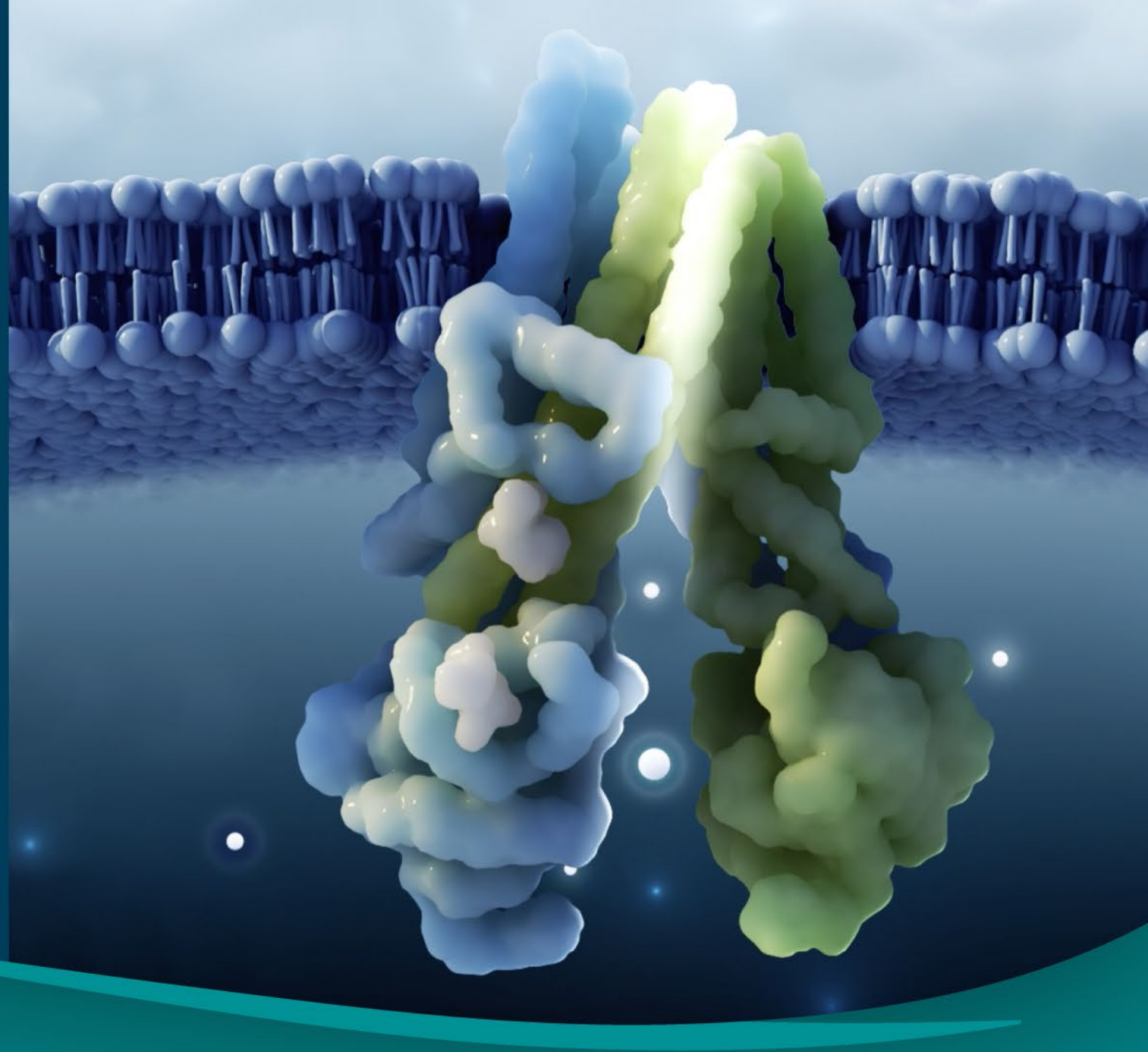
Sionna Therapeutics

PreciSION CF Key Learnings and Plans to Advance Dual Combination

September 14th, 2026



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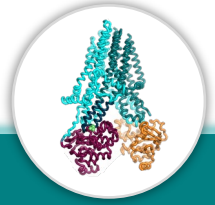
We have strong conviction in the NBD1 biology, and believe there is compelling rationale to pursue the dual combination



Post hoc observations provide evidence of NBD1 target engagement & biology

In post hoc analysis, removing clear confounders, SION-719 improved mean sweat chloride up to -8.6 mmol/L

Combination with Trikafta® may have blunted NBD1 impact

4-drug combination may have limited NBD1 impact due to lower Trikafta exposures and a potential interaction with the potentiator, ivacaftor

Dual combination advancing to Ph 2a POC

We believe SION-451 + SION-2222 has the potential to deliver a compelling new CF treatment option

Cash preservation actions taken

~$268M cash as of 2Q26; 46% workforce reduction and cost saving initiatives expected to extend cash runway into 2H29, supporting execution of dual combo strategy

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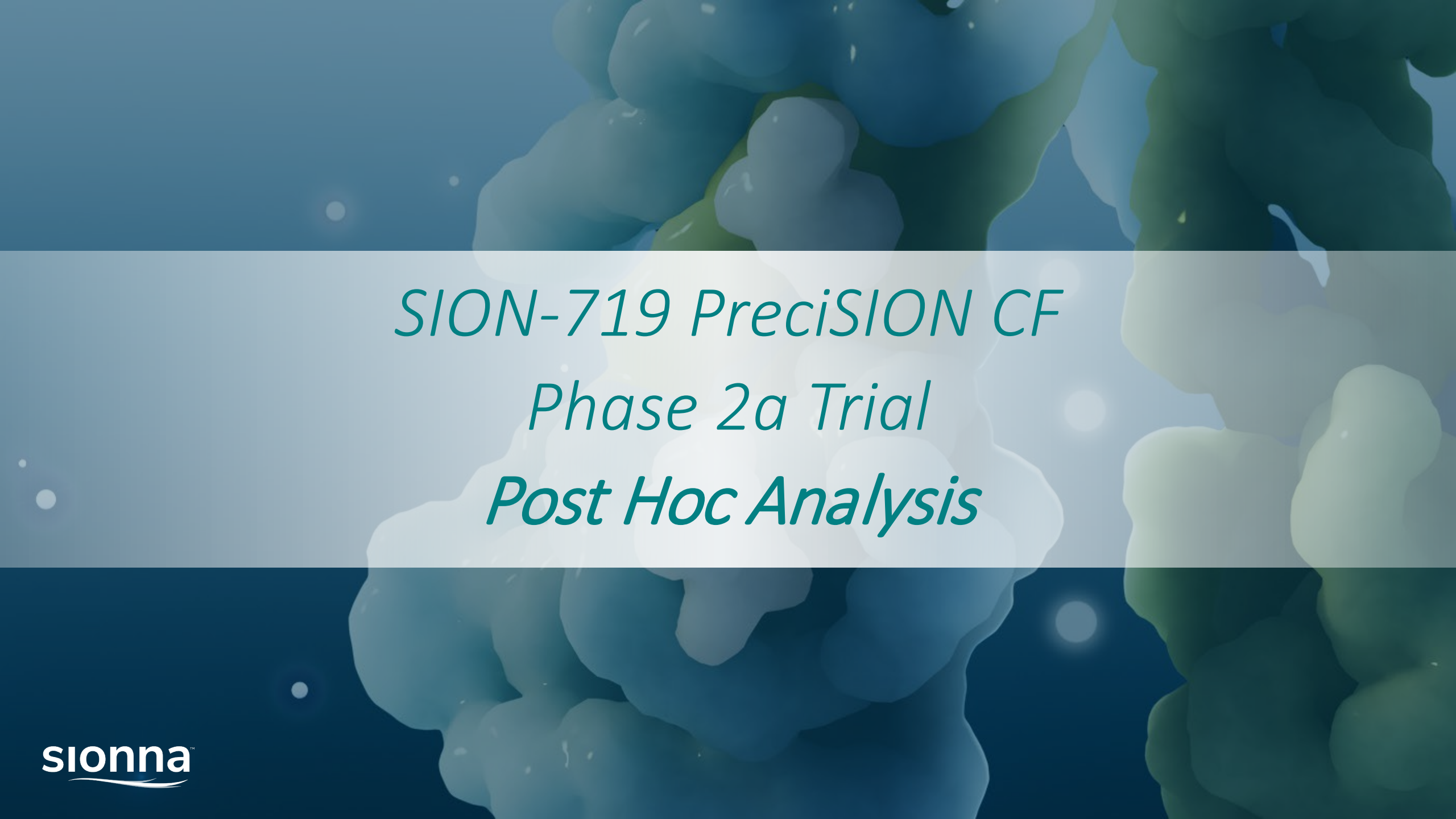
NBD1 - Nucleotide Binding Domain 1 of CFTR (CF transmembrane conductance regulator)
CF – Cystic Fibrosis; Ph – Phase; POC – proof-of-concept
Trikafta is a registered trademarks of Vertex Pharmaceuticals Incorporated



SION-719 PreciSION CF Phase 2a Trial

Post Hoc Analysis

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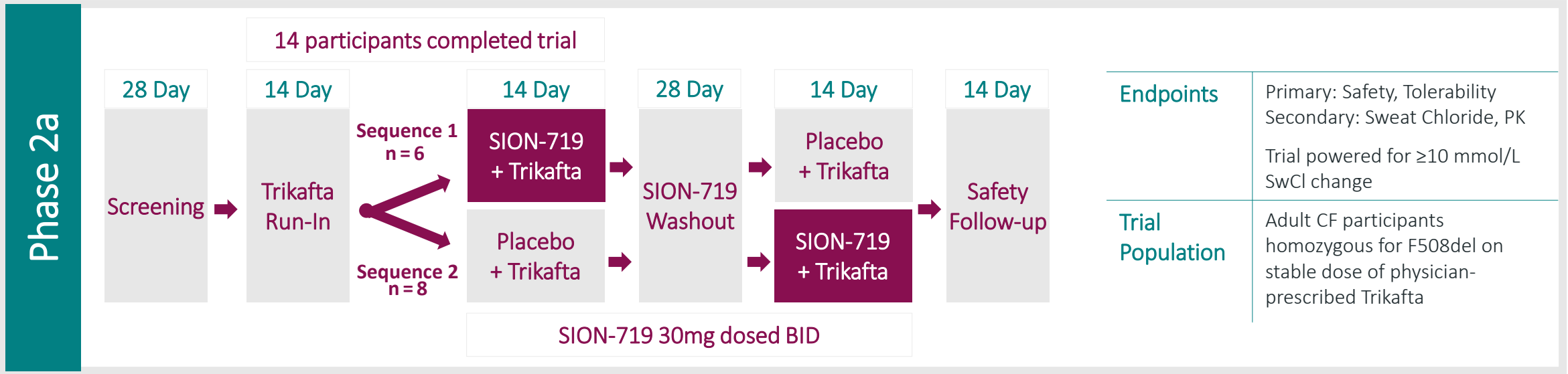
PreciSION CF Phase 2a trial used a randomized, double-blind crossover design to evaluate SION-719 added to background Trikafta



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

We believe period-specific baselines better account for PK & SwCl variability observed in trial

BID – twice a day; SwCl – sweat chloride; PK – pharmacokinetics
MMRM – Mixed Model with Repeated Measures

Multiple dimensions of the PreciSION CF post hoc analysis consistently 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

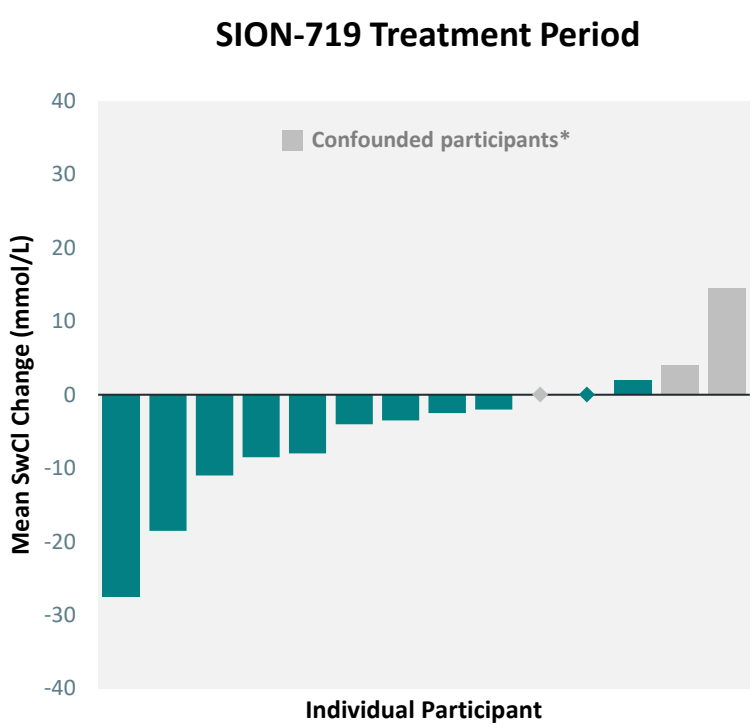
SION-719 + ETI showed high CFTR current before stimulation in nonclinical assay

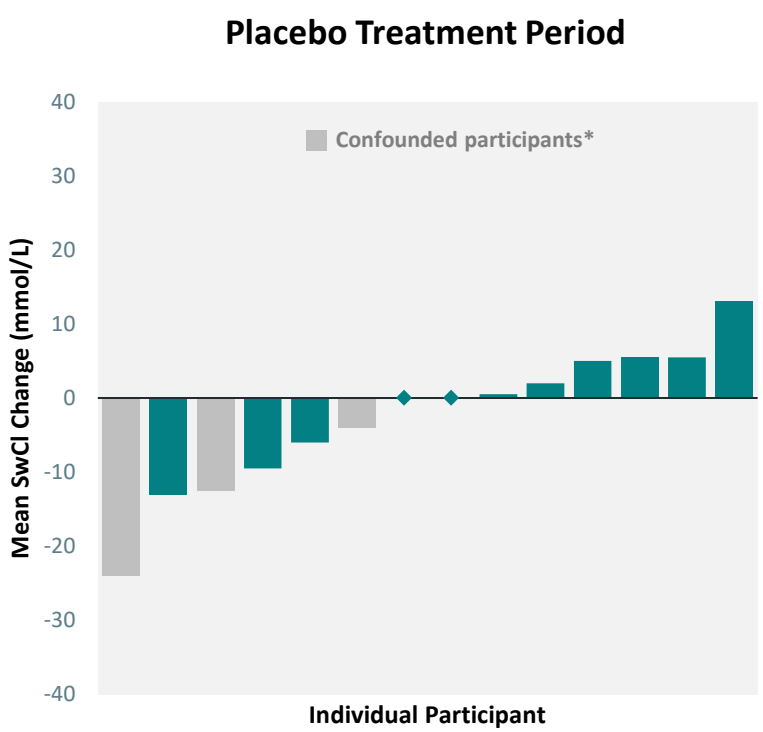
Four-drug combination potentially limited response by dysregulating the CFTR channel

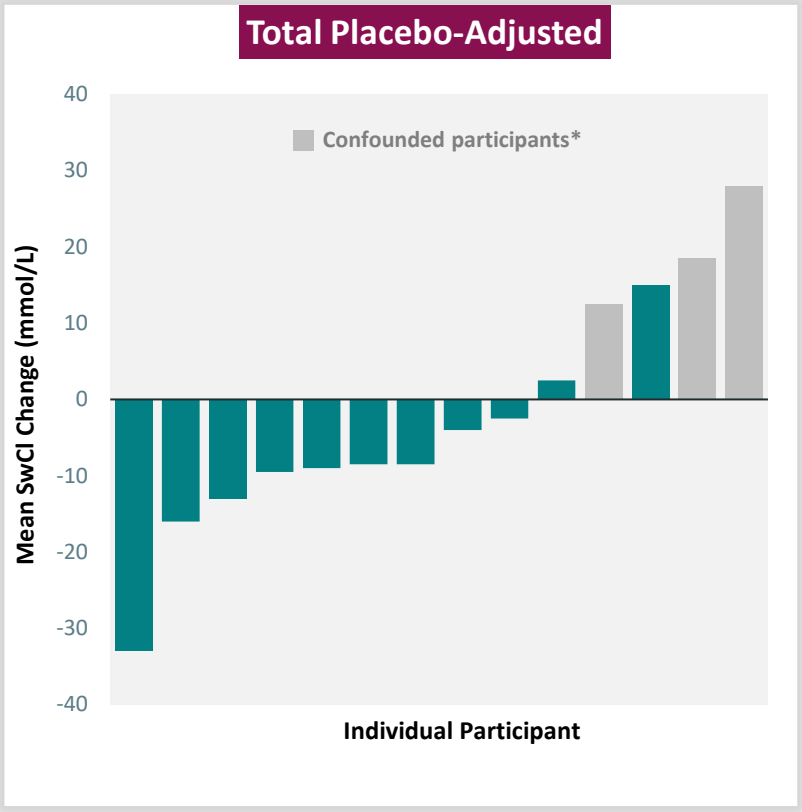
ETI – elexacaftor/tezacaftor/ivacaftor, the components of Trikafta

The placebo-adjusted sweat chloride outcome was very different than what we expected

Secondary SwCl analysis - full data set (N=14)







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

*3 participants with PK patterns consistent with dosing non-adherence

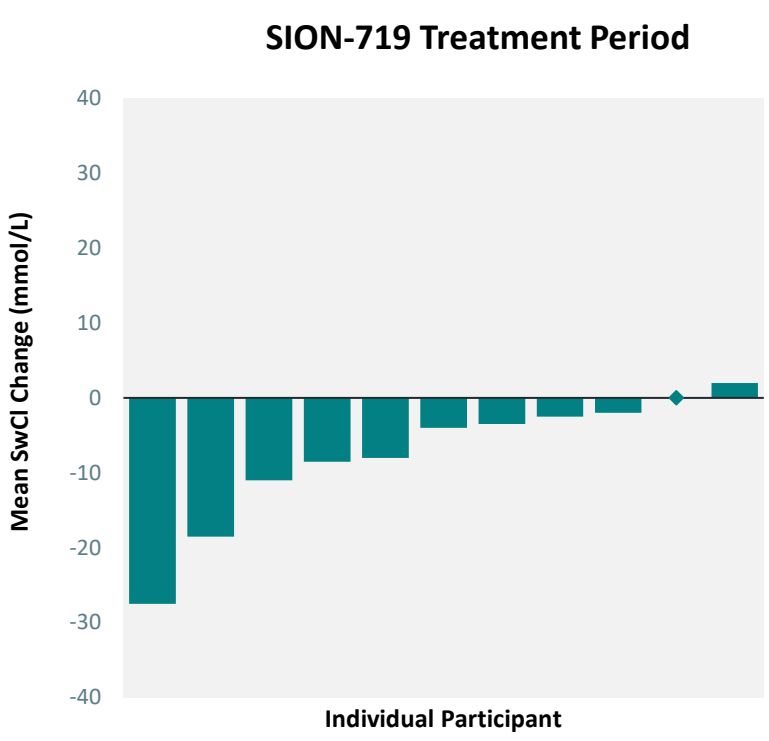
A deep dive into the data identified patterns in 3 participants consistent with dosing non-adherence that may have confounded results

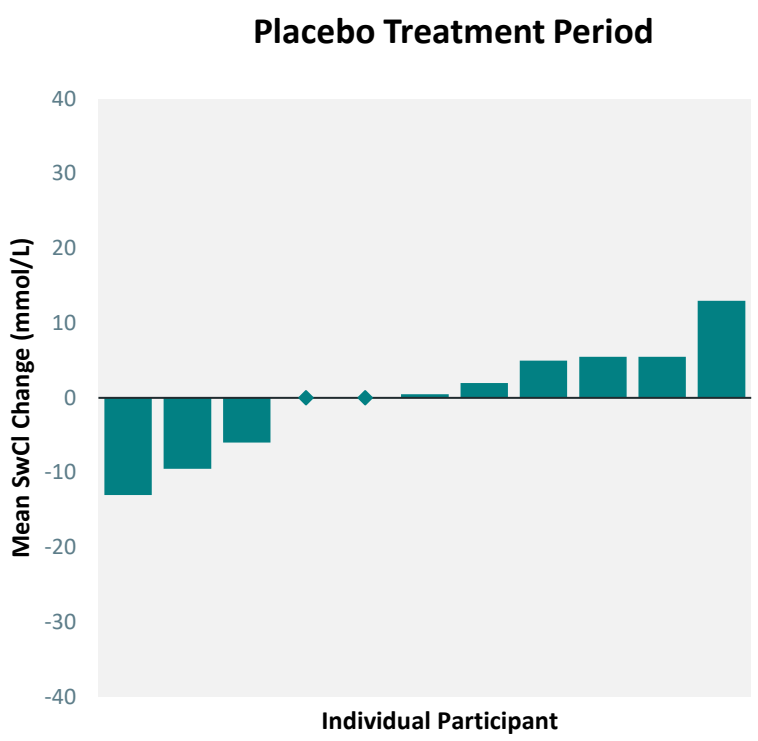
Observation	Study Impact
1 participant with unmeasurable Trikafta and 1 participant with unusually low levels of Trikafta after washout at start of placebo period	Believed to have caused direct and confounding placebo SwCl response of -24.0 and -12.5 mmol/L
1 participant with unmeasurable SION-719 at the end of the treatment period	Believed to have caused direct and confounding increase in SwCl of +14.5 mmol/L during SION-719 treatment period

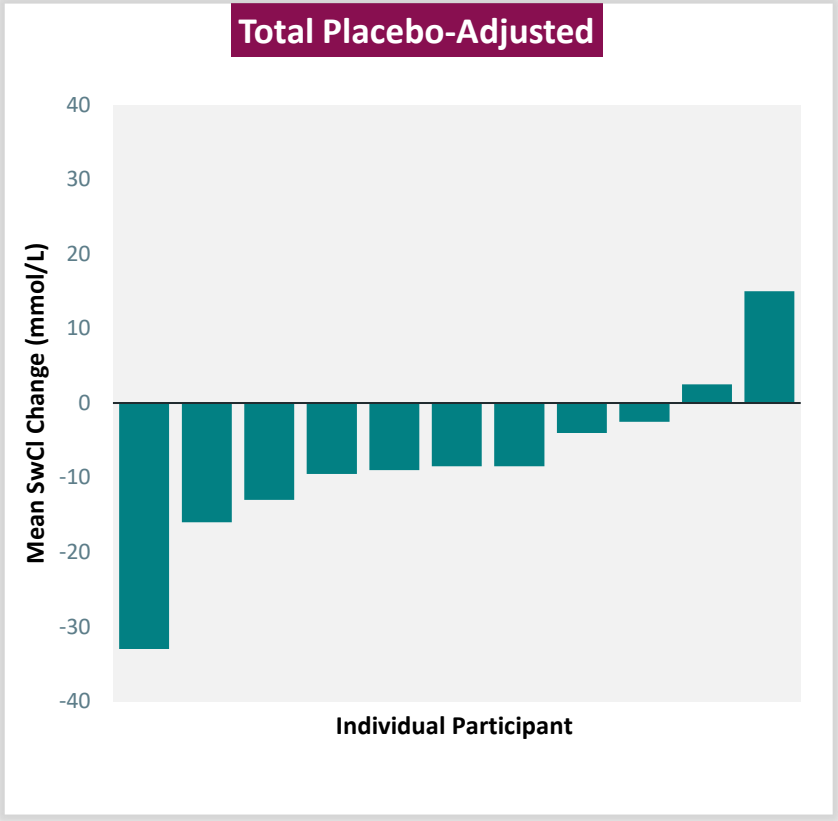
No other participants identified with these patterns consistent with dosing non-adherence

Removing 3 confounded participants, the post hoc treatment and placebo data indicate NBD1 stabilization

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



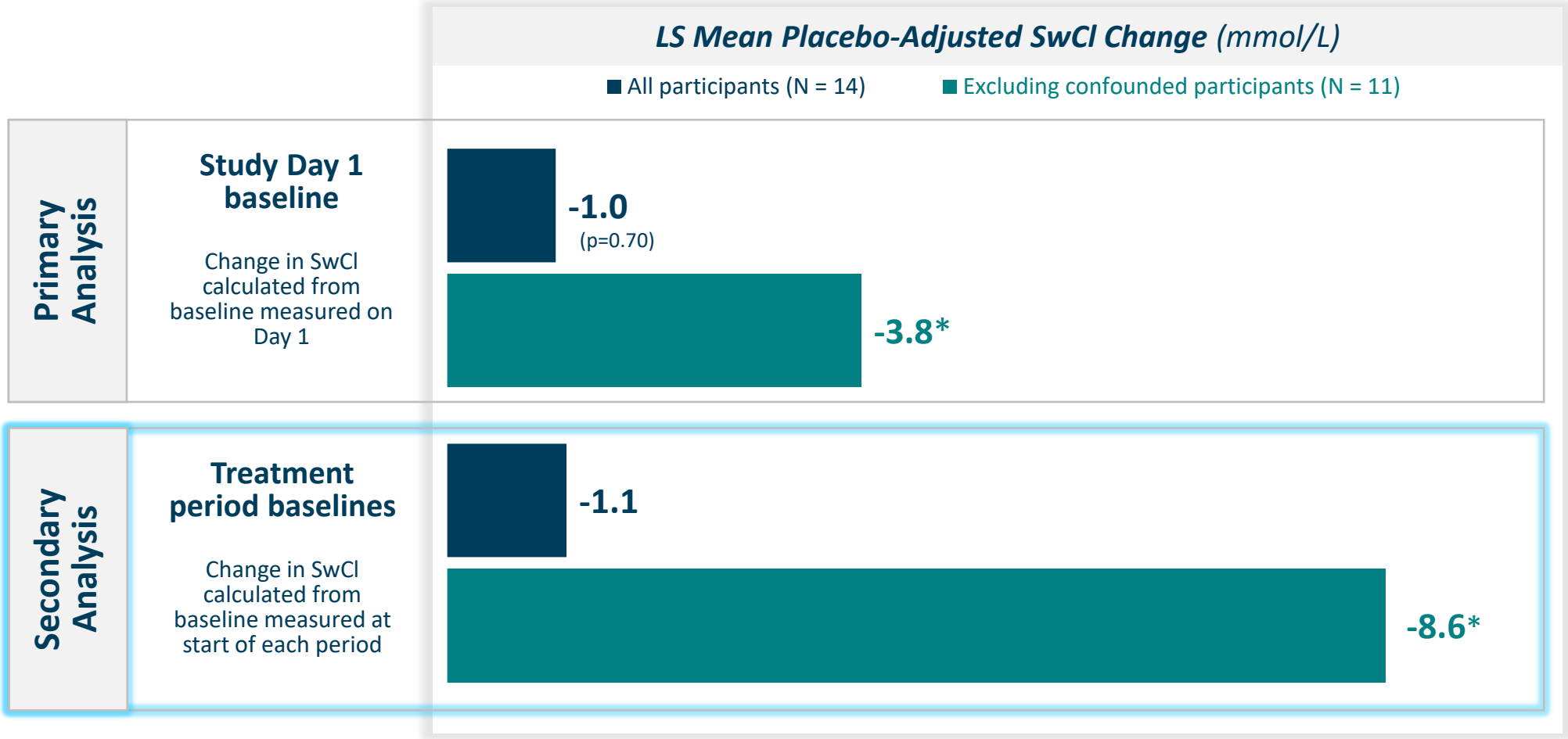




Note: End of placebo-period values were imputed for two participants with missing observations. Participants are ordered within each panel by magnitude of sweat chloride change.

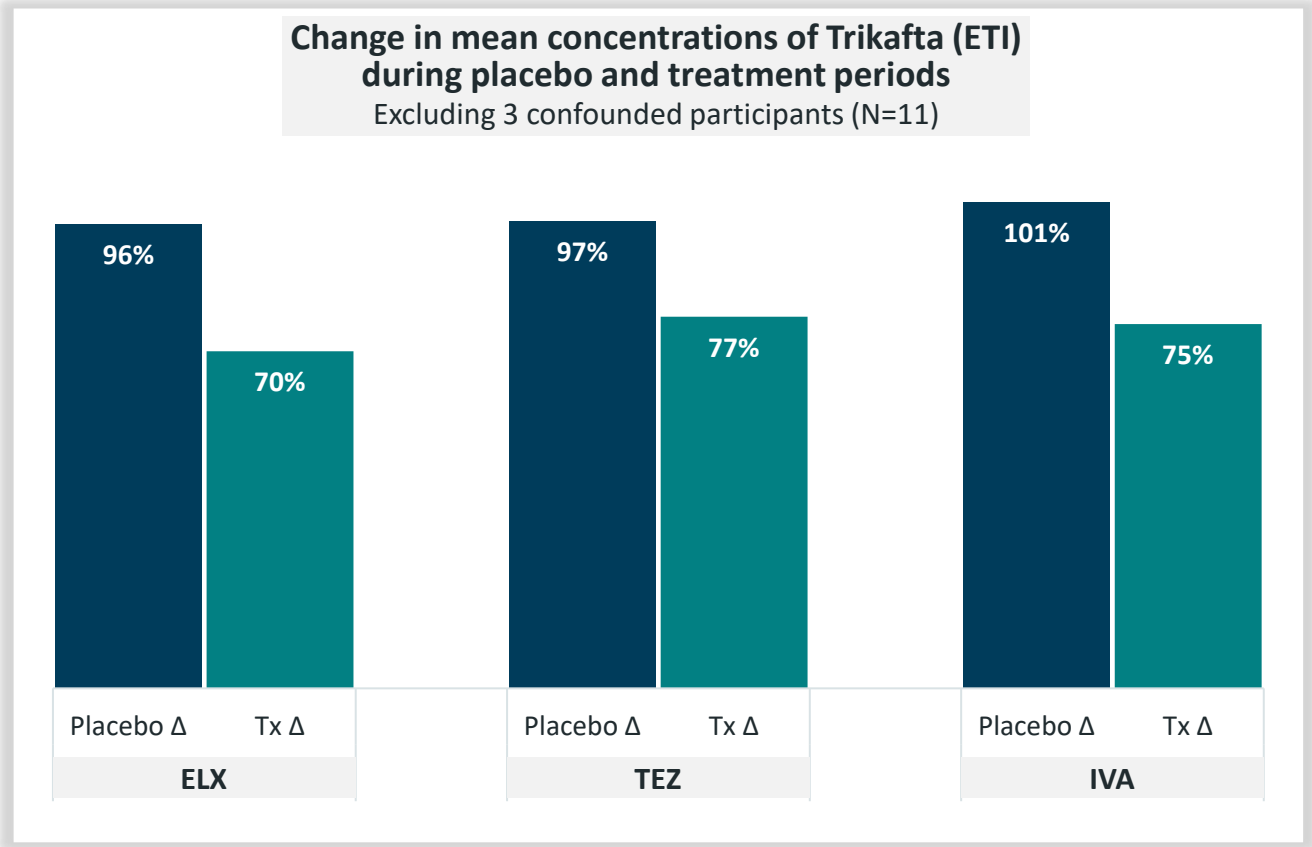
Individual SwCl changes calculated from each treatment period baseline

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

However, we expected a larger treatment effect – this may have been due to lower Trikafta exposures when combined with SION-719



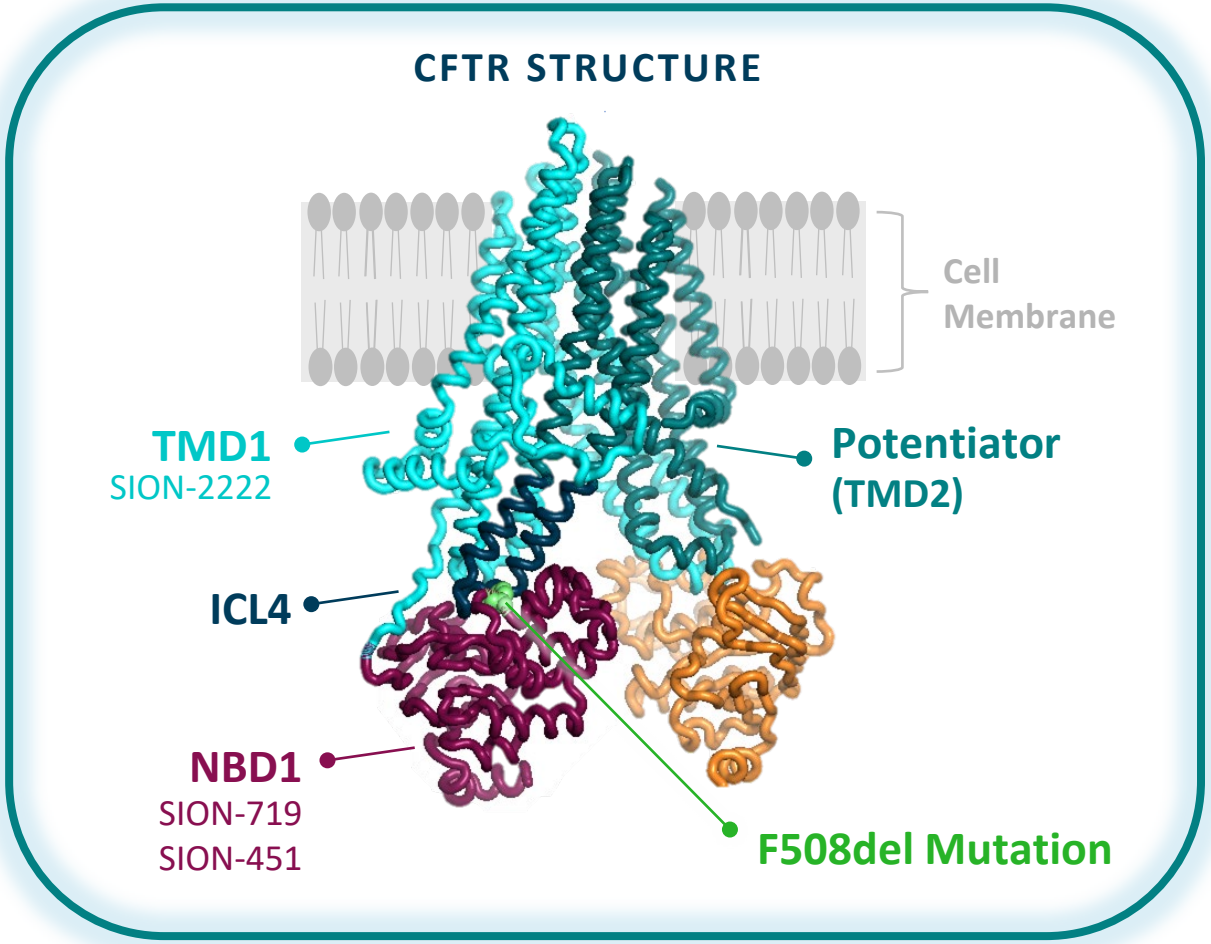
Key observations

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 modulators target distinct regions of CFTR, and work in different ways to restore function



TMD1 and ICL4 Correctors help CFTR fold properly, reach the cell surface and remain more stable there by targeting regions around NBD1

NBD1 stabilizers directly target NBD1, where F508del resides[1]. We believe stabilizing NBD1 is critical to CFTR folding, trafficking and function

Potentiators increase channel opening, enabling greater chloride transport through CFTR

1. Thibodeau 2010

ICL4 – Intracellular Loop 4 of CFTR; TMD – Transmembrane Domain 1 and 2 of CFTR

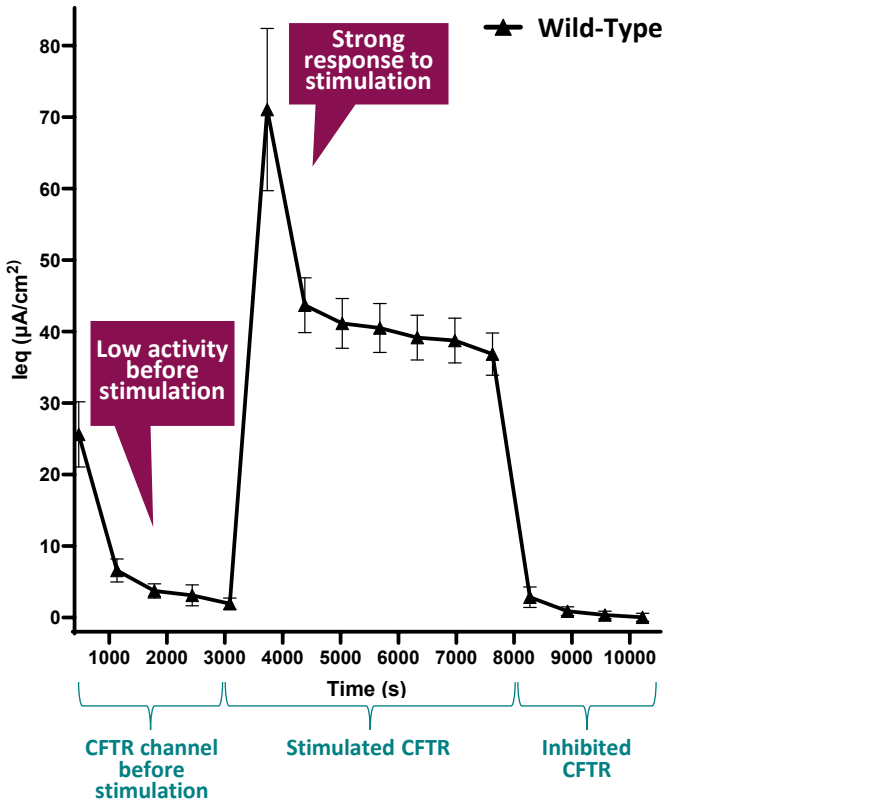
PreciSION CF outcome informed an emerging hypothesis regarding CFTR channel behavior when NBD1 is combined with a potentiator

Nonclinical data:	**Add-On** **SION-719** NBD1 + **ETI** SOC	**Dual Combination** **SION-451** NBD1 **SION-2222** TMD1
Protein Maturation	**Restored up to wild-type**	**Restored up to wild-type**
Trafficking	**Restored up to wild-type**	**Restored up to wild-type**
Half-life	**Restored up to wild-type**	**Restored up to wild-type**
CFHBE stimulated current	**Restored up to wild-type**	**Restored up to wild-type**
CFHBE pre-stimulated current	**Higher than wild-type**	**Wild-type levels**

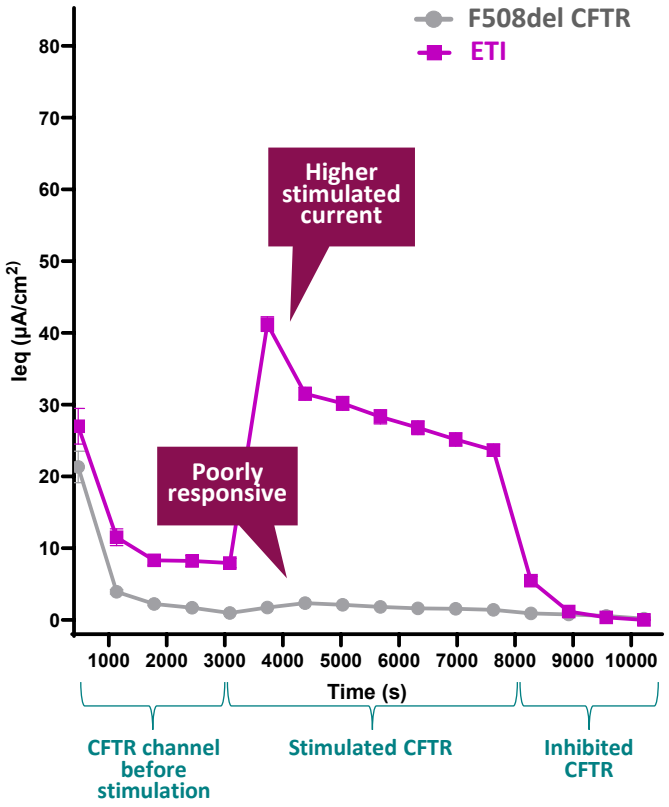
Note: all data from Sionna conducted nonclinical studies
CFHBE – CF Human Bronchial Epithelial primary cells; SOC – standard of care

CFTR channel activity in CFHBE model: normal and CF cells with ETI

Normal regulation



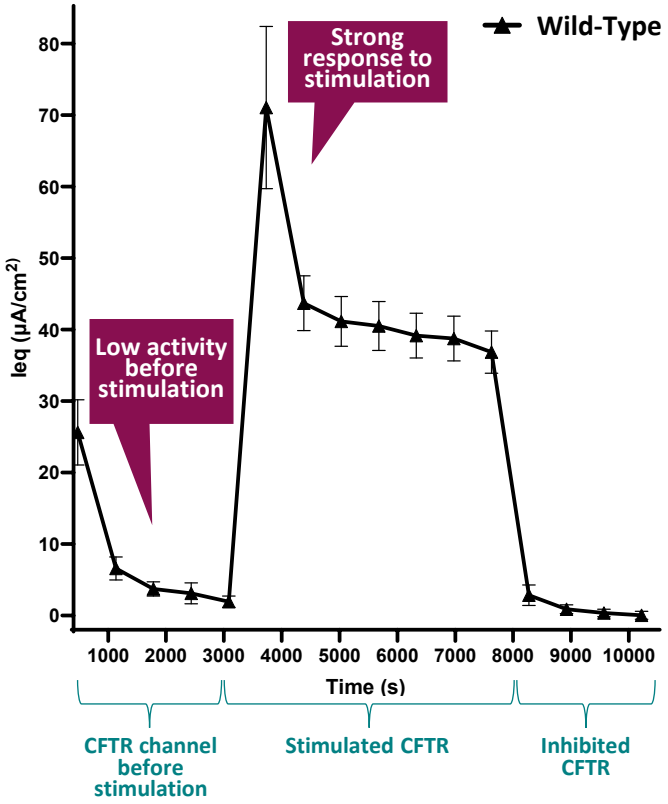
ETI modulated F508del-CFTR at E_{max}



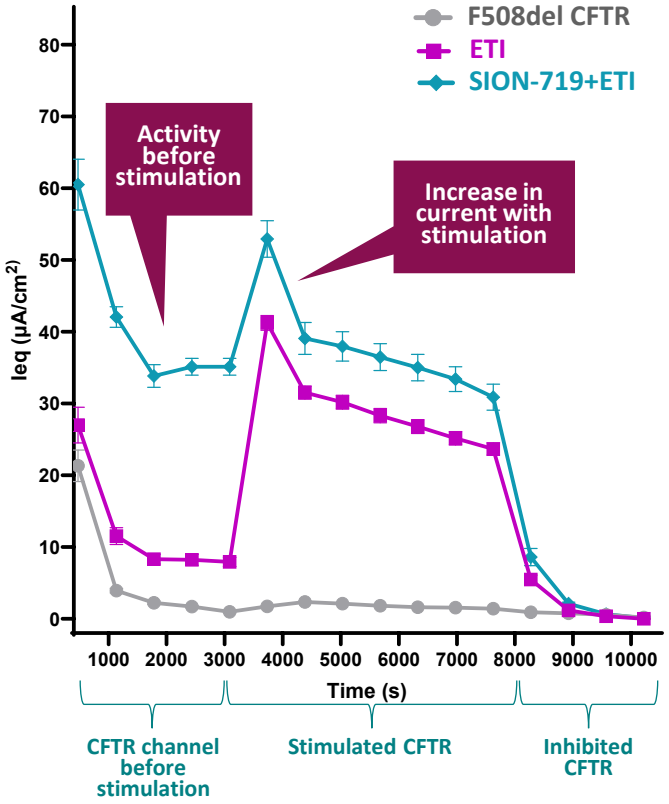
Note: F508del-CFTR and wild-type traces shown each represent a single donor with 4 replicates, and are representative of the observed profiles from 6 donors in the same experiment

CFTR channel activity in CFHBE model: normal and CF cells with SION-719 (NBD1) + ETI

Normal regulation



SION-719 + ETI modulated F508del-CFTR at E_{max}

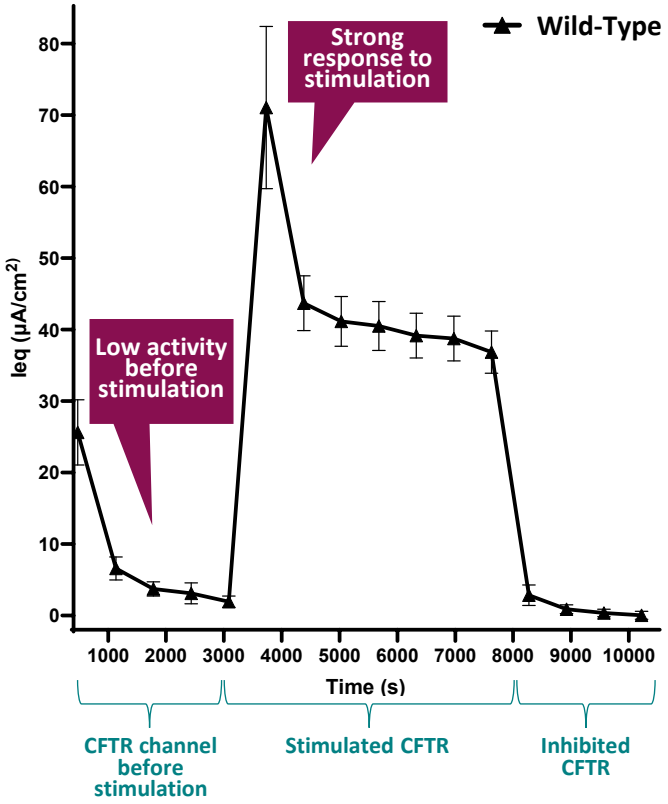


Note: F508del-CFTR and wild-type traces shown each represent a single donor with 4 replicates, and are representative of the observed profiles from 6 donors in the same experiment

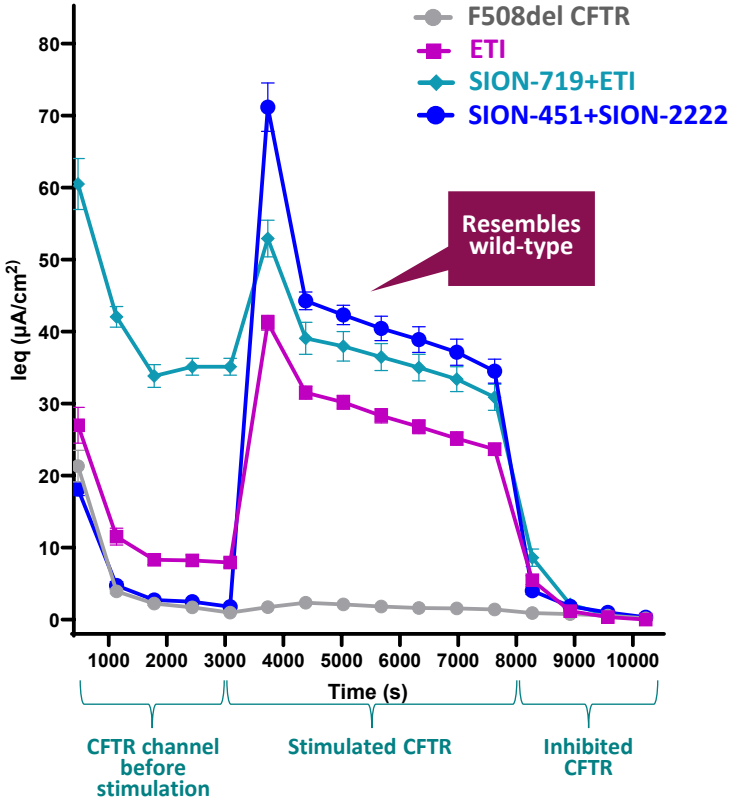
30mg of '719 pre stimulated current is ~50% of E_{max}

CFTR channel activity in CFHBE model: normal and CF cells with SION-451 (NBD1)+ SION-2222 (TMD1)

Normal regulation



Dual combination modulated F508del-CFTR 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

SION-451 Dual Combination

Next Steps

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

High Unmet Need

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

Many patients on SOC experience **tolerability challenges like liver side effects or CNS burden**[4,5]

More Options Desired

CF is **a one-player, ~$13B market** today[6], expected to grow to **~$15B-17B** by 2030[7]

Current SOC are all built on the same mechanisms of action **and do not directly stabilize NBD1**

1. Konstan, NACFC poster 2022; 2. Zemanick, JCF 2024; 3. Normal sweat chloride <30 mmol/L
4. Alyftrek USPI (March 2026); 5. Trikafta USPI (March 2026);
6. VRTX 2Q26 earnings call; 7. 2025 Wall Street research estimates
CNS – central nervous system

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

Trial Design & Conduct

- Evaluated safety, tolerability, and PK across multiple dose combinations of SION-451 + SION-2222 and SION-451 + SION-109 in healthy volunteers
- 3:1 randomized, double-blind, placebo-controlled cohorts
- All cohorts dosed for 14 days
- Cohorts dosed in fasted conditions, except 1 cohort in each dual combination administered with food

60 total participants dosed (5 cohorts)

60 total participants dosed (5 cohorts)

Trial Outcome

- Achieved safety and tolerability objectives
- Exceeded PK target at go-forward doses
- Combination PK was consistent with respective single agent Phase 1 profiles
- SION-451 + SION-2222 identified as preferred combination based on target coverage
- Data support advancement of SION-451 + SION-2222 as a potential next-generation dual combination
- PreciSION CF learnings are informing next phase of development

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

Trial Participants (n)	Placebo (n=15)	SION-451 BID + SION-2222 QD 3 cohorts (n=27)	SION-451 BID + SION-2222 BID 2 cohorts (n=18)	Total (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

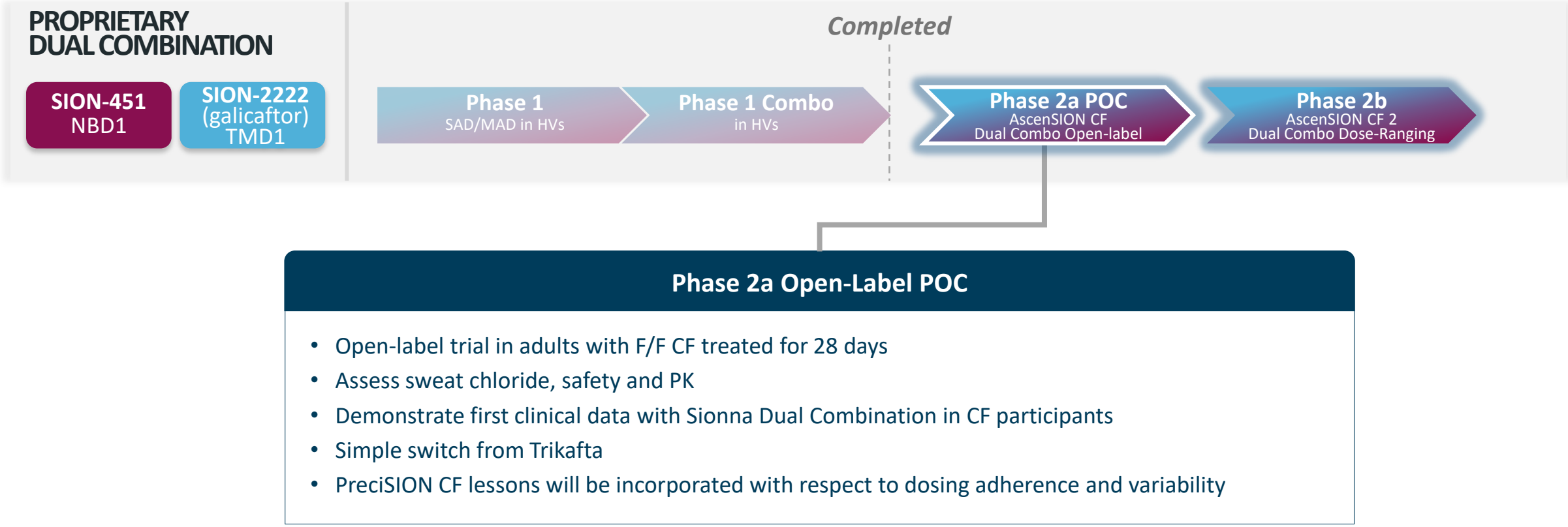
SION-451 BID + SION-2222 BID

- 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]

QD – once a day

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

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

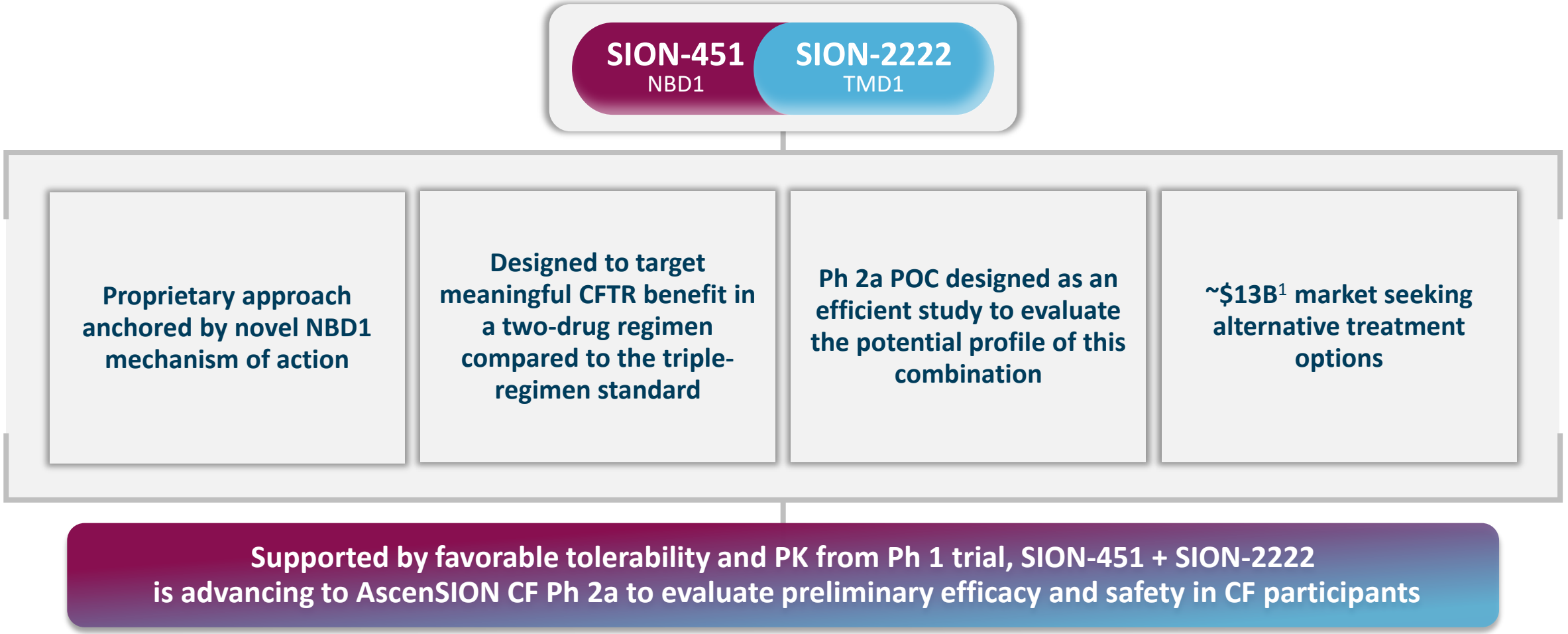


Phase 2a Open-Label POC

- Open-label trial in adults with F/F CF treated for 28 days
- Assess sweat chloride, safety and PK
- Demonstrate first clinical data with Sionna Dual Combination in CF participants
- Simple switch from Trikafta
- PreciSION CF lessons will be incorporated with respect to dosing adherence and variability

SAD – single ascending dose; MAD – multiple ascending dose; HV – healthy volunteer
F/F – homozygous for F508del mutation

Dual combination offers a differentiated two-drug approach to current triple-combination therapies



1. VRTX 2Q26 earnings call

Q&A

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