

NBD1 is a novel target in Cystic Fibrosis

Clinical Learnings and Research Data

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Presenter Disclosure

Greg Sawicki, MD

There following relationship(s) exist(s) related to this presentation:

- Sionna Therapeutics, Lead Study PI and Clinical Advisor
- Vertex, Consultant

Steve Altmann, Director of Research

- Steve Altmann is an employee of Sionna Therapeutics



PreciSION CF

Phase 2a, Placebo-Controlled Cross-Over Study of SION-719 added to ELX/TEZ/IVA in People with CF

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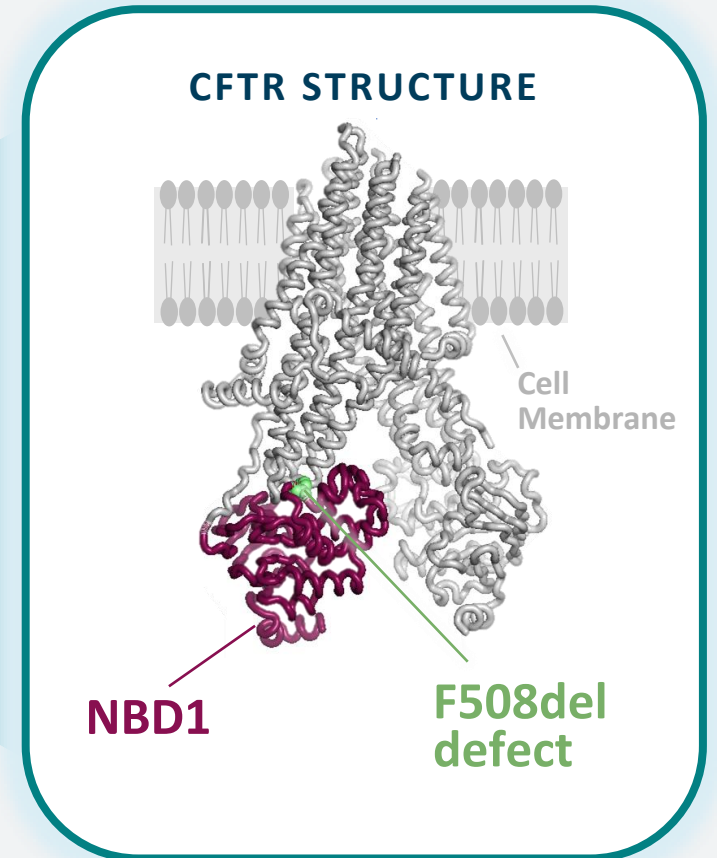
NBD1 stabilization is a potentially differentiated approach to restoring F508del-CFTR function

Cystic Fibrosis And NBD1 Biology

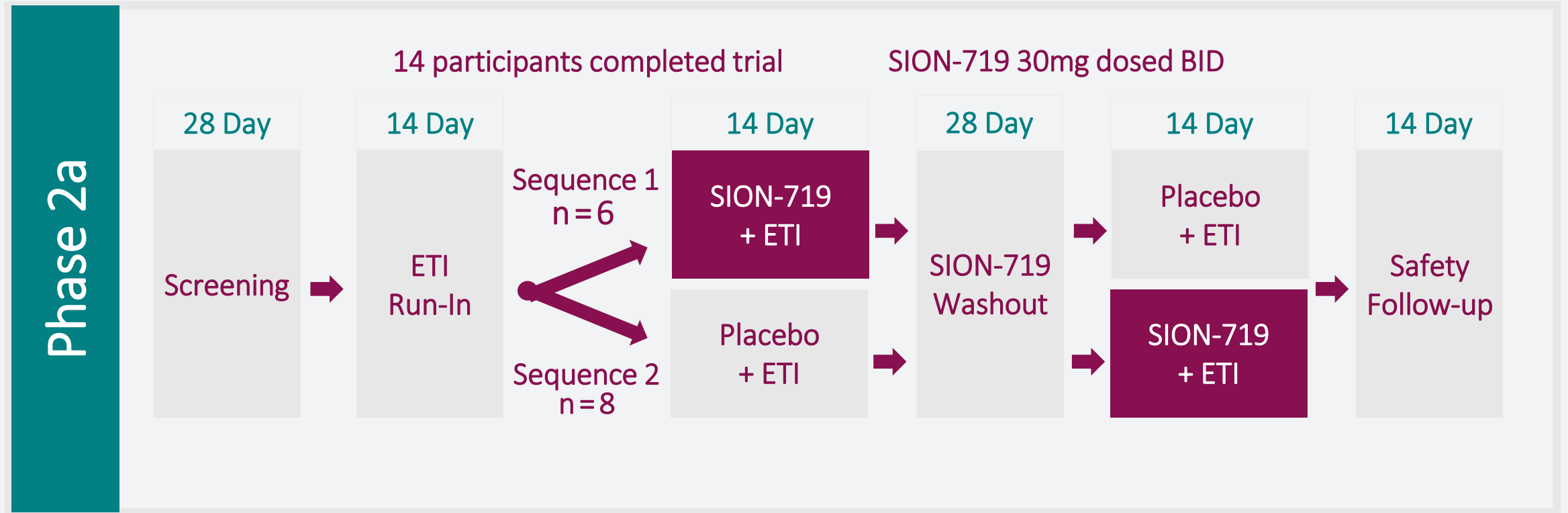
F508del defect resides within the NBD1 domain and severely destabilizes NBD1, preventing normal CFTR function

Sionna NBD1 stabilizers are *novel small molecules that directly bind to and stabilize NBD1* at physiological concentrations in nonclinical models

NBD1 stabilizers, combined with other modulators that improve domain-domain assembly, have the *potential to further improve F508del-CFTR function*



PreciSION CF Ph2a trial design: randomized, double-blind crossover design to evaluate SION-719 added to background ETI



BID – twice a day

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

Population, Endpoints & Analysis

Trial Population

- Adults with CF
- Homozygous for F508del on stable dose of physician-prescribed ETI
- SwCl 45-80 (inclusive)

Primary Analysis

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

Endpoints

- Primary: Safety, Tolerability
- Secondary: Sweat Chloride, PK

Secondary Analysis

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

MMRM - Mixed Model Repeated Measures



Summary of baseline and demographic characteristics

	Overall N=15
Age, years, mean (SD)	35.1 (7.9)
Sex [n (%)]	
Female	7 (46.7)
Male	8 (53.3)
Ethnicity [n (%)]	
Non- Hispanic or Latino	15 (100)
Race	
White	15 (100)
BMI (kg/m ²) [mean (SD)]	25.5 (3.3)
Sweat Chloride (mmol/L) [mean (SD)]	56.5 (10.5)

SD – standard deviation; BMI – body mass index

SION-719 was generally well tolerated when added to ETI with most TEAEs mild to moderate

	Placebo			SION-719 30mg BID		
	Sequence 1 N=6	Sequence 2 N=8	Overall N=14	Sequence 1 N=7*	Sequence 2 N=8	Overall N=15*
Trial Participants (n)						
Total number of TEAEs	3	20	23	8	14	22
Participants with any TEAE, n (%)	3 (50%)	4 (50%)	7 (50%)	5 (71%)	7 (88%)	12 (80%)
Mild (Grade 1)	2 (33%)	2 (25%)	4 (29%)	3 (43%)	5 (63%)	8 (53%)
Moderate (Grade 2)	1 (17%)	2 (25%)	3 (21%)	2 (29%)	1 (13%)	3 (20%)
Severe (Grade 3)	-	-	-	-	1 (13%)	1 (7%)
Leading to treatment discontinuation	-	-	-	-	-	-
Serious TEAEs, n (%)	-	-	-	-	-	-
Participants with liver function test associated TEAE	1 (17%)	1 (13%)	2 (14%)	-	2 (25%)	2 (13%)

- Most TEAEs were mild to moderate, and no SAEs
- No meaningful trends in LFTs. One grade 3 LFT was observed at end of washout period pre-dosing, which resolved over the course of SION-719 treatment
- 1 participant discontinued, unrelated to an adverse event

TEAE – treatment-emergent adverse event; SAE – serious adverse event; LFT – liver function test
Sequence 1= 719→placebo; Sequence 2= placebo→719

*includes 1 participant who discontinued for reasons not related to treatment

PreciSION CF Pharmacodynamic & Pharmacokinetic Results

Primary Analysis Change in SwCl

Mean placebo-adjusted sweat chloride change of -1.0 mmol/L ($p = 0.7$)

PK Exposure

SION-719 exposure in the study was consistent with single agent PK

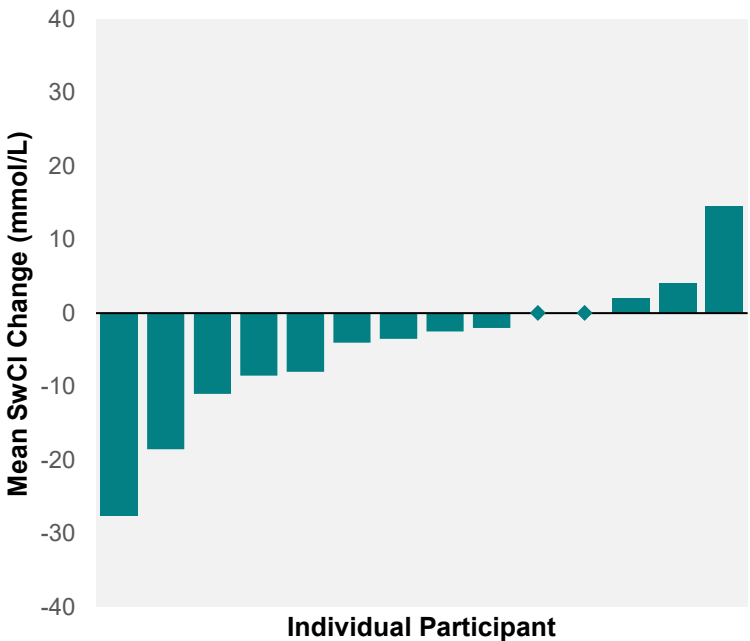
Mean ETI exposures were consistent with published data; however, ETI exposures, on average, declined during SION-719 period while they remained generally stable during placebo period

ETI - elexacaftor/tezacaftor/ivacaftor, the components of Trikafta
PK - pharmacokinetic
SwCl - sweat chloride

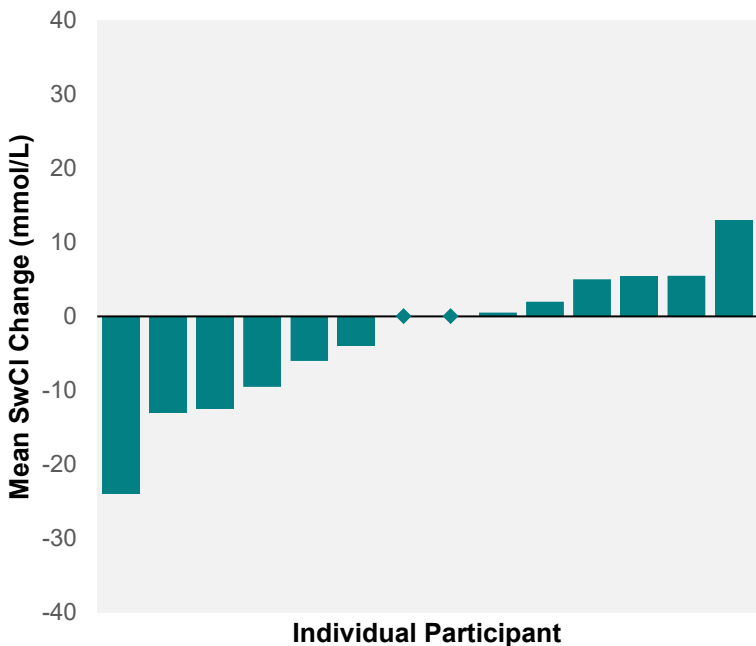
Sweat chloride change within-period for all participants

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

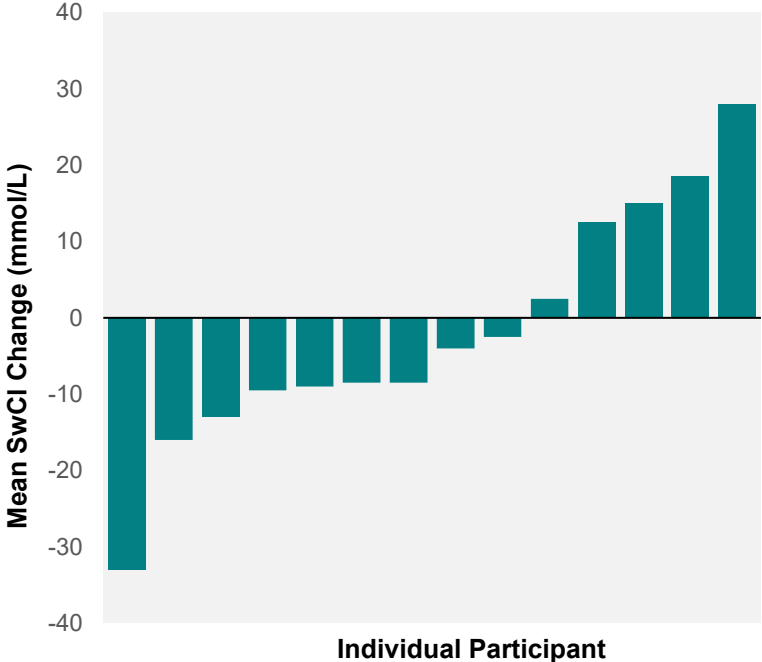
SION-719 Treatment Period



Placebo Treatment Period



Total Placebo-Adjusted



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

Three key potential confounding factors identified in a post-hoc analysis

1

PK Outliers

Three participants had no or unusually low SION-719 or ETI 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
PK – pharmacokinetic

PK outliers confounded ability to assess treatment effect

1

PK Outliers

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

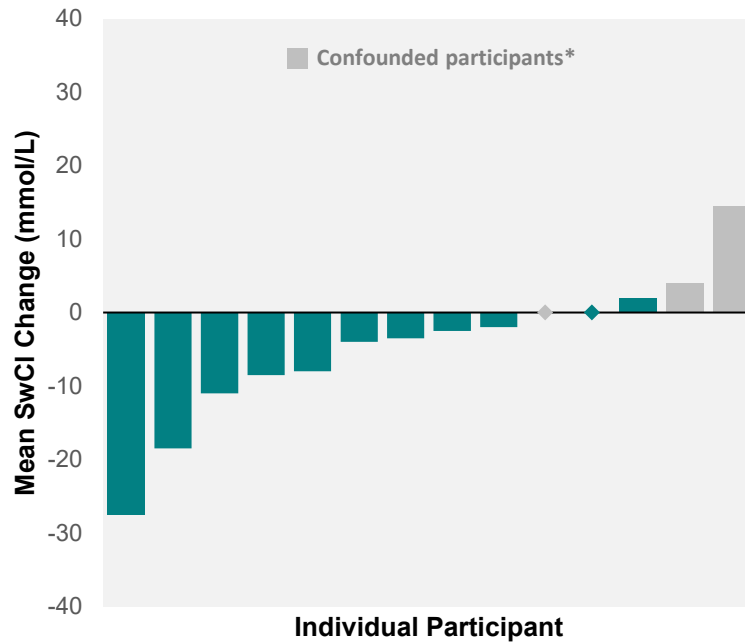
- Two participants had *low to undetectable ETI concentrations* at beginning of placebo period which increased to normal ETI concentrations at end of placebo period – resulted in *large placebo effect* on SwCl
- One participant had *undetectable SION-719 concentrations* at end of SION-719 period, impacting ability to assess SION-719 treatment effect

ETI: elexacaftor/tezacaftor/ivacaftor, the components of Trikafta
SwCl - sweat chloride

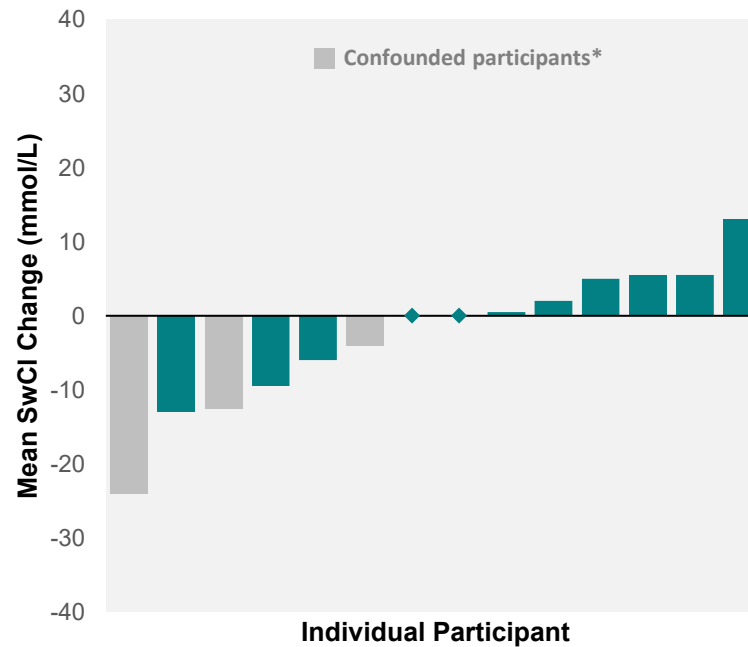
Post-Hoc SwCl data showing the 3 PK outliers

Secondary SwCl analysis - excluding 3 PK outliers (N=14)

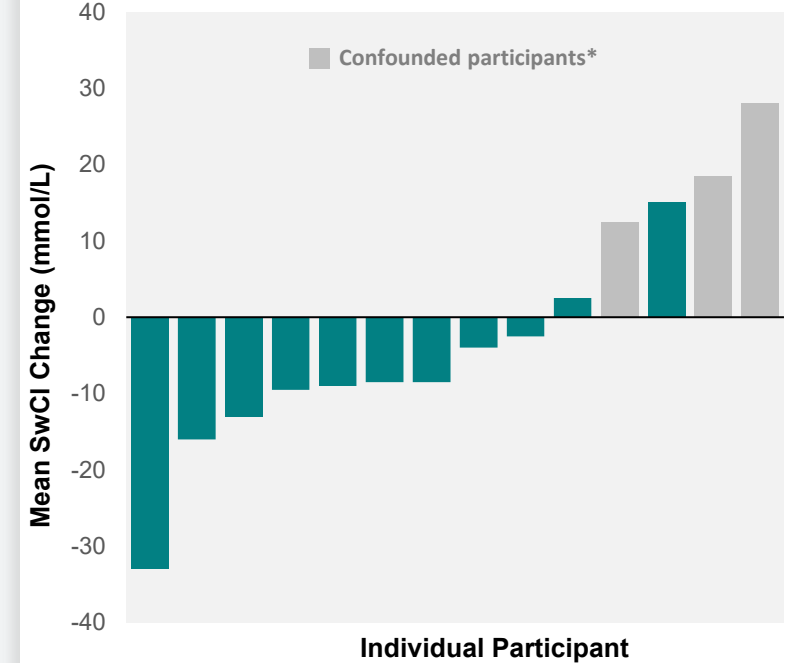
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Placebo Treatment Period



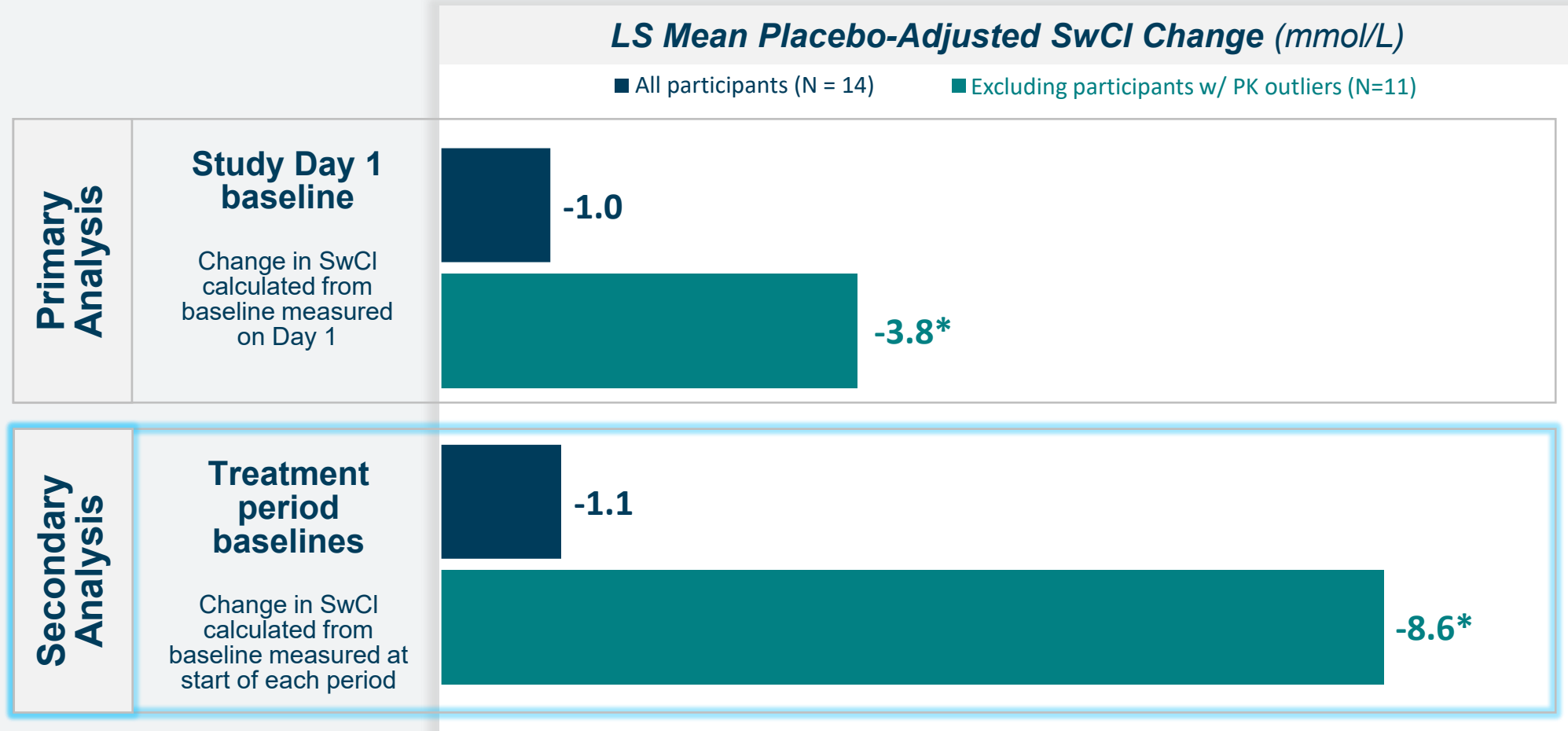
Total Placebo-Adjusted



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Individual SwCl changes calculated from each treatment period baseline
*3 participants with PK patterns consistent with dosing non-adherence

Analysis of placebo-adjusted mean sweat chloride change



*Post-hoc analysis

ETI exposure decreased on average during SION-719 period but not during placebo period

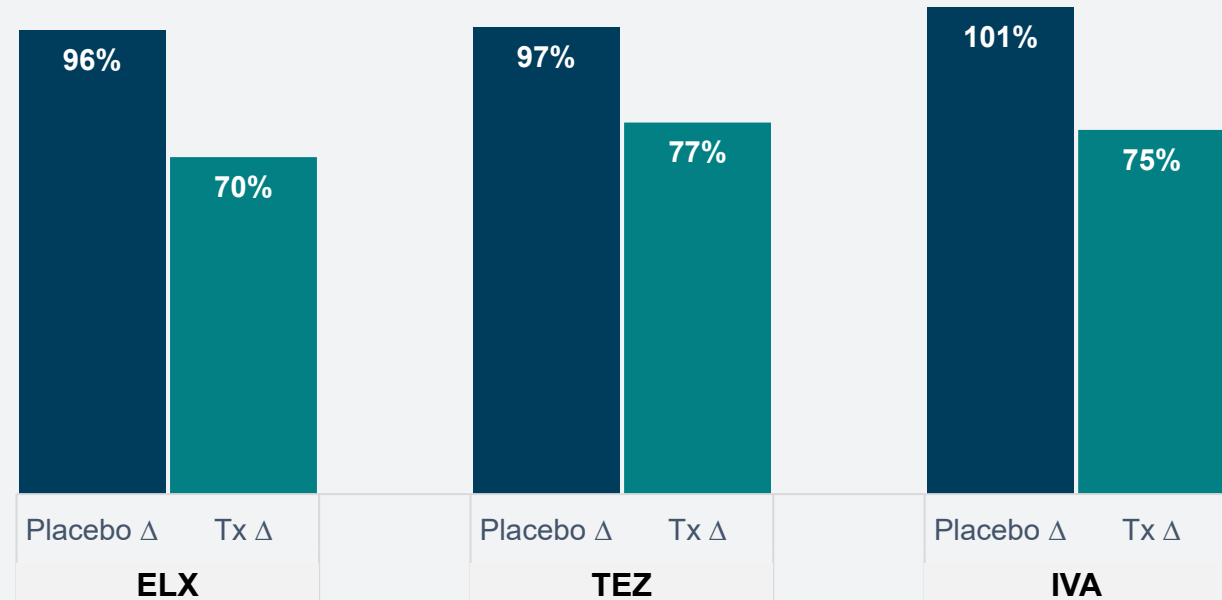
2

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

ELX/TEZ/IVA drug concentration at end of treatment periods relative to beginning of treatment period (%)
excluding 3 PK outliers (N=11)



ETI: elexacaftor/tezacaftor/ivacaftor, the components of Trikafta
ELX: Ellexacaftor; TEZ: tezacaftor; IVA: ivacaftor
Tx: Treatment

Conclusions

- SION-719 was *generally well-tolerated when added to ETI* in people with CF and F508del homozygous genotype
- *In primary analysis*, SION-719 added to ETI resulted in a placebo-adjusted change in SwCl of -1.0 mmol/L
- *Post hoc analysis* removing the 3 PK outliers demonstrated a *placebo-adjusted within-period change in SwCl of -8.6mmol/L* when SION-719 was added to ETI, and provides evidence of NBD1 target engagement

**Thanking the participants,
investigators and their
teams**

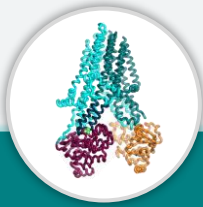


Dual combinations anchored by NBD1 stabilizers in nonclinical models have demonstrated the potential to improve F508del-CFTR function up to wild-type levels

A novel and differentiated approach from PreciSION-CF

Steve Altmann, Director of Research
Sionna Therapeutics

We have strong conviction in the NBD1 biology, and advancing SION-451 + SION-2222 combination to Phase 2a



Post hoc observations of PreciSION CF trial provide evidence of NBD1 target engagement & biology



Combination with Trikafta® may have blunted NBD1 impact



Novel dual combination advancing to Phase 2a proof-of-concept

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

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

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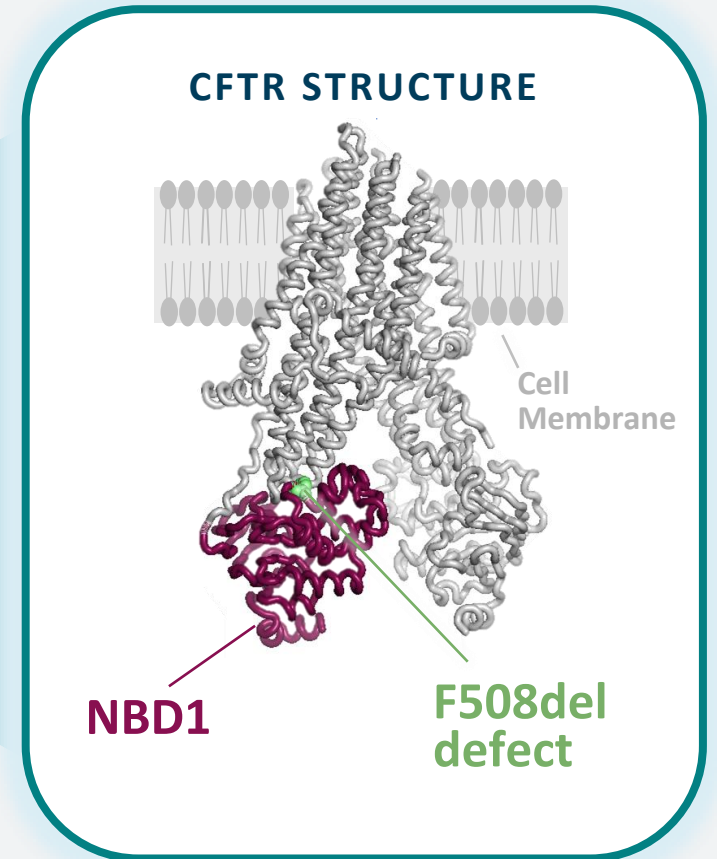
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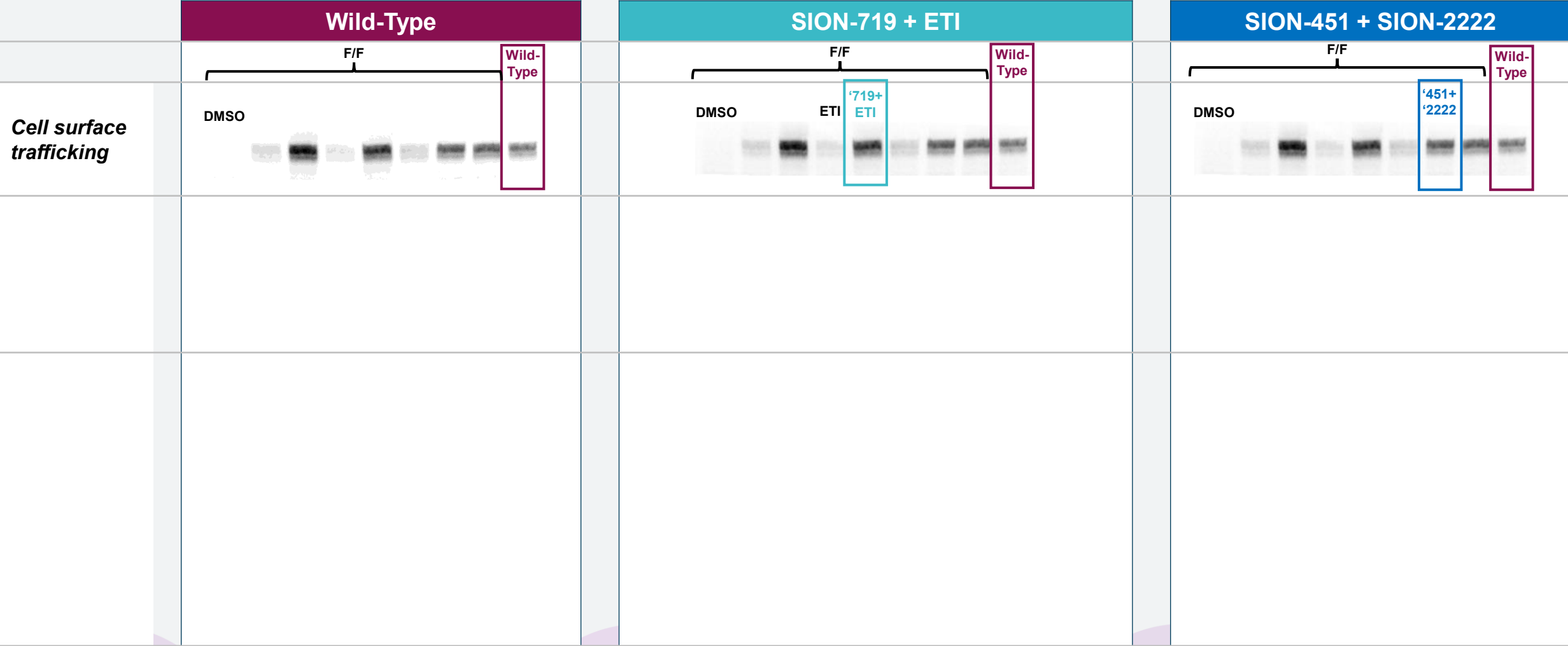
F508del defect resides within the NBD1 domain and severely destabilizes NBD1, preventing normal CFTR function

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NBD1 stabilizers, combined with other modulators that improve domain-domain assembly, have the *potential to further improve F508del-CFTR function*



Combinations with NBD1 stabilizers, SION-719 or SION-451, bring more F508del CFTR to cell surface in CFHBEs at E_{max}



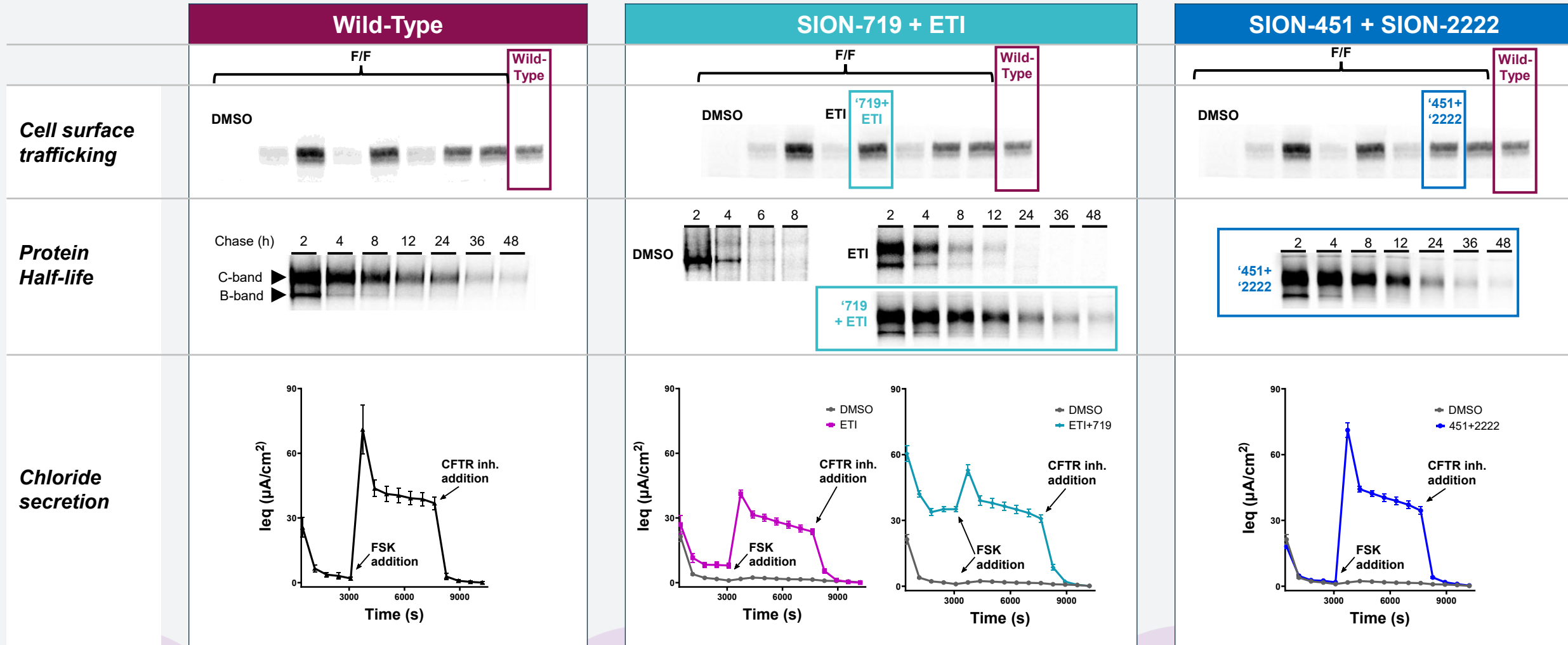
See **Poster 295**, “Assessing the effect of NBD1 stabilizers SION-451 and SION-719 in combination with other CFTR modulators in primary human bronchial epithelial cells from F508del/F508del and F508del/null donors”, NACFC 2026, S. Altmann

NBD1 stabilizers can correct F508del CFTR half-life up to normal levels in CFHBEs at E_{max}



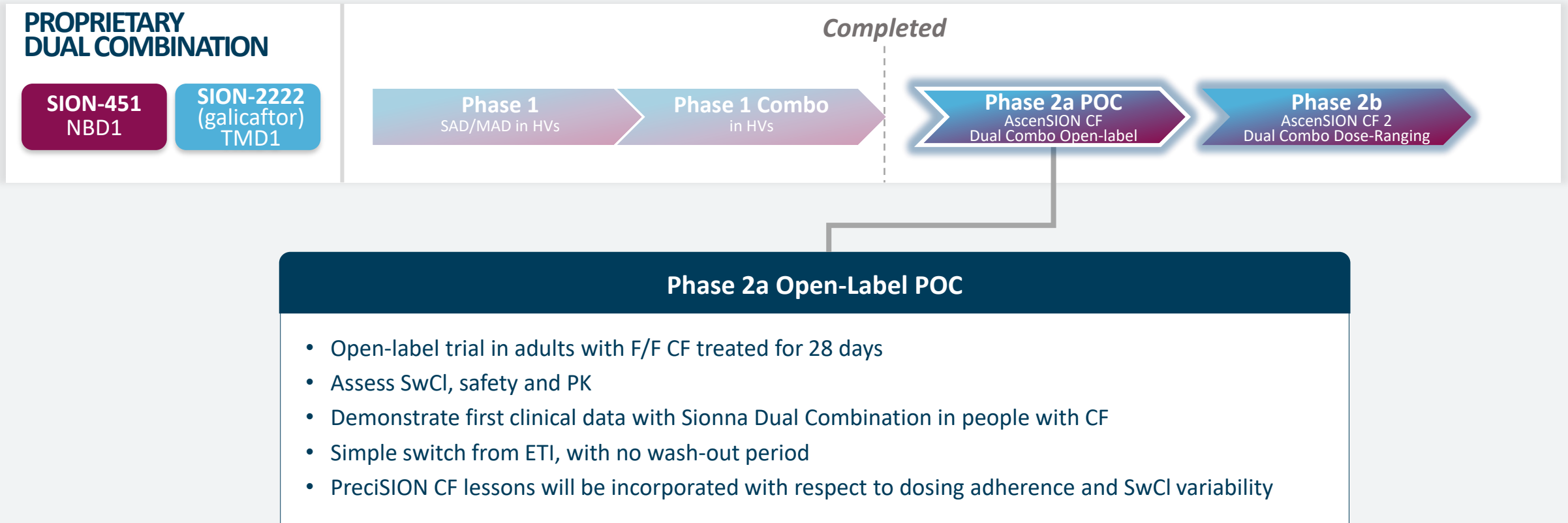
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SION-451 + SION-2222 improve CFTR function to normal levels and behaves similar to wild type in CFHBEs at E_{max}



See **Poster 295**, "Assessing the effect of NBD1 stabilizers SION-451 and SION-719 in combination with other CFTR modulators in primary human bronchial epithelial cells from F508del/F508del and F508del/null donors", NACFC 2026, S. Altmann

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
ETI – ellexacaftor/tezacaftor/ivacaftor
F/F – homozygous for F508del mutation
PK – pharmacokinetics
SwCl – sweat chloride

Thank you!

