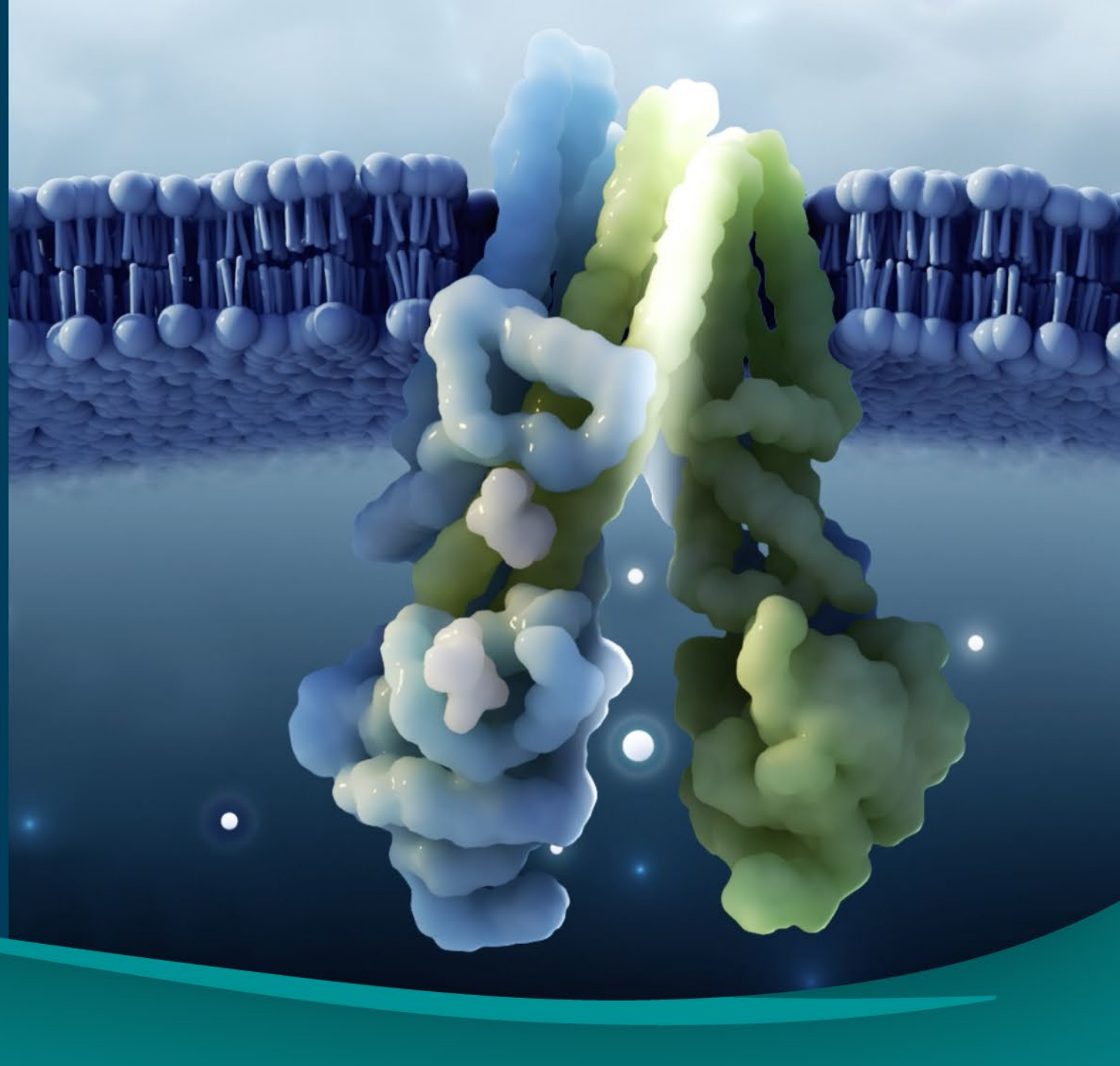
Sionna Therapeutics

Topline Data from Two NBD1 Stabilizer Programs

August 10, 2026



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Key takeaways from today's announcement

PreciSION CF Phase 2a did not meet key activity endpoint

- The trial demonstrated a -1.0 mmol/L mean placebo-adjusted sweat chloride change (p = 0.7) when SION-719 was added to Trikafta®
- We are not advancing development of SION-719 as an add-on to SOC
- We will continue to analyze the results of PreciSION CF, including potential confounding factors

SION-451 dual combination program

- The Phase 1 dual combination trial achieved the safety, tolerability, and PK objectives that we had defined prior to the Phase 2a PreciSION CF results
- Continued evaluation of the SION-719 data will inform the next steps for the SION-451 clinical program

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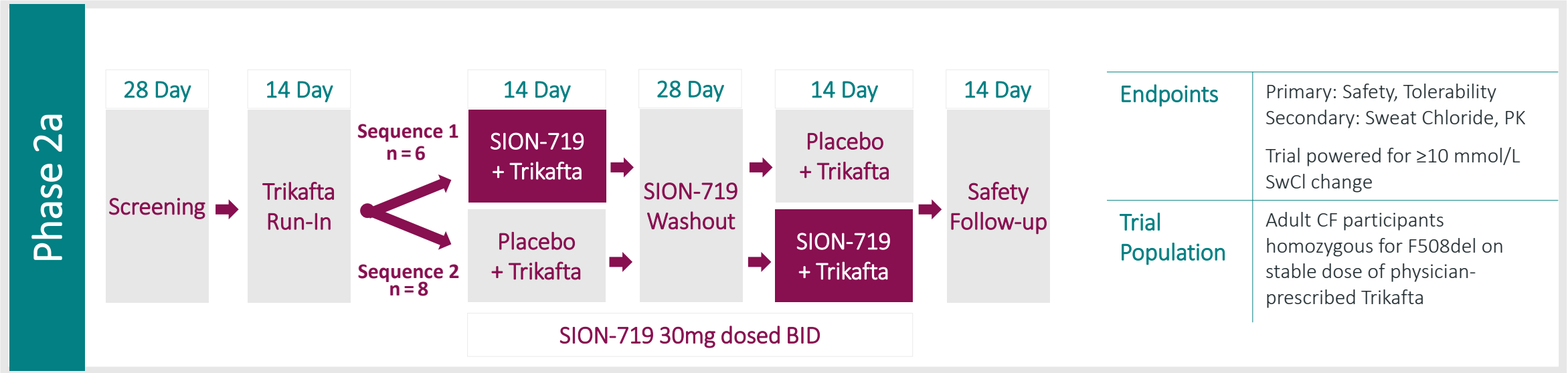
CF – Cystic Fibrosis; SOC – standard of care
PK – pharmacokinetics
Trikafta is a registered trademark of Vertex Pharmaceuticals Incorporated

Agenda

1. **SION-719 PreciSION CF Phase 2a Proof-of-Concept Trial**
   Topline Results
2. **SION-451 Phase 1 Healthy Volunteer Dual Combination Trial**
   Topline Results
3. **Closing Remarks**
4. **Q&A**

PreciSION CF Phase 2a proof-of-concept trial evaluated SION-719 when added to 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 plan

- Primary sweat chloride analysis compared patient change from baseline during SION-719 and placebo treatment periods using an MMRM method
- Safety analysis was a description of adverse events reported by each treatment group within each period

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

Summary of baseline and demographic characteristics

PreciSION CF enrolled adult CF participants homozygous for F508del
who were stable on Trikafta for at least 3 months before screening

	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

PreciSION CF Phase 2a proof-of-concept trial results

Key Activity Endpoint	Mean placebo-adjusted sweat chloride change of -1.0 mmol/L (p = 0.7) when patients were taking a 30mg BID dose of SION-719 on background of Trikafta Potential trial confounders were observed, including SwCl variability, and differences in Trikafta exposure levels between the SION-719 and placebo periods
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 Mean Trikafta exposures were consistent with published data; however, there were trends of lower Trikafta exposure in the SION-719 treated periods, which we believe were driven by individual variability

As a result of today's data, we are not advancing SION-719 as an add-on to SOC

We continue to evaluate the impact of potential confounders on the interpretation of the trial data

AE – adverse event

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

	Placebo			SION-719 30mg BID		
Trial Participants (n)	**Sequence 1** *N=6*	**Sequence 2** *N=8*	**Overall** *N=14*	**Sequence 1** *N=7**	**Sequence 2** *N=8*	**Overall** *N=15**
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 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

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Phase 1 clinical evaluation of SION-451 anchored dual combinations

Trial Design & Conduct

- Evaluated the safety, tolerability, and PK profiles of different 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

- Trial achieved its safety, tolerability, and PK objectives, including target exposures defined prior to the Phase 2a PreciSION CF results
- SION-451 + SION-2222 identified as preferred combination based on target coverage. PK of this combination was consistent with single agent Phase 1 data
- Actively assessing results of PreciSION CF, including our translational framework, to help characterize the potential profile of the SION-451 + SION-2222 dual combination

NBD1 – Nucleotide Binding Domain 1 of CFTR
TMD – Transmembrane Domain 1 and 2 of CFTR; ICL4 – Intracellular Loop 4 of CFTR

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

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Next steps for Sionna following today's clinical results

NEXT STEPS

Sionna does not plan to advance SION-719 as an add-on to SOC

We will continue to analyze the results of the SION-719 PreciSION CF study, and assess implications for the SION-451 dual combination program

CASH CONSIDERATIONS

~$268 million in cash and cash equivalents as of 2Q26

Plan to take action to preserve capital while evaluating next steps

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