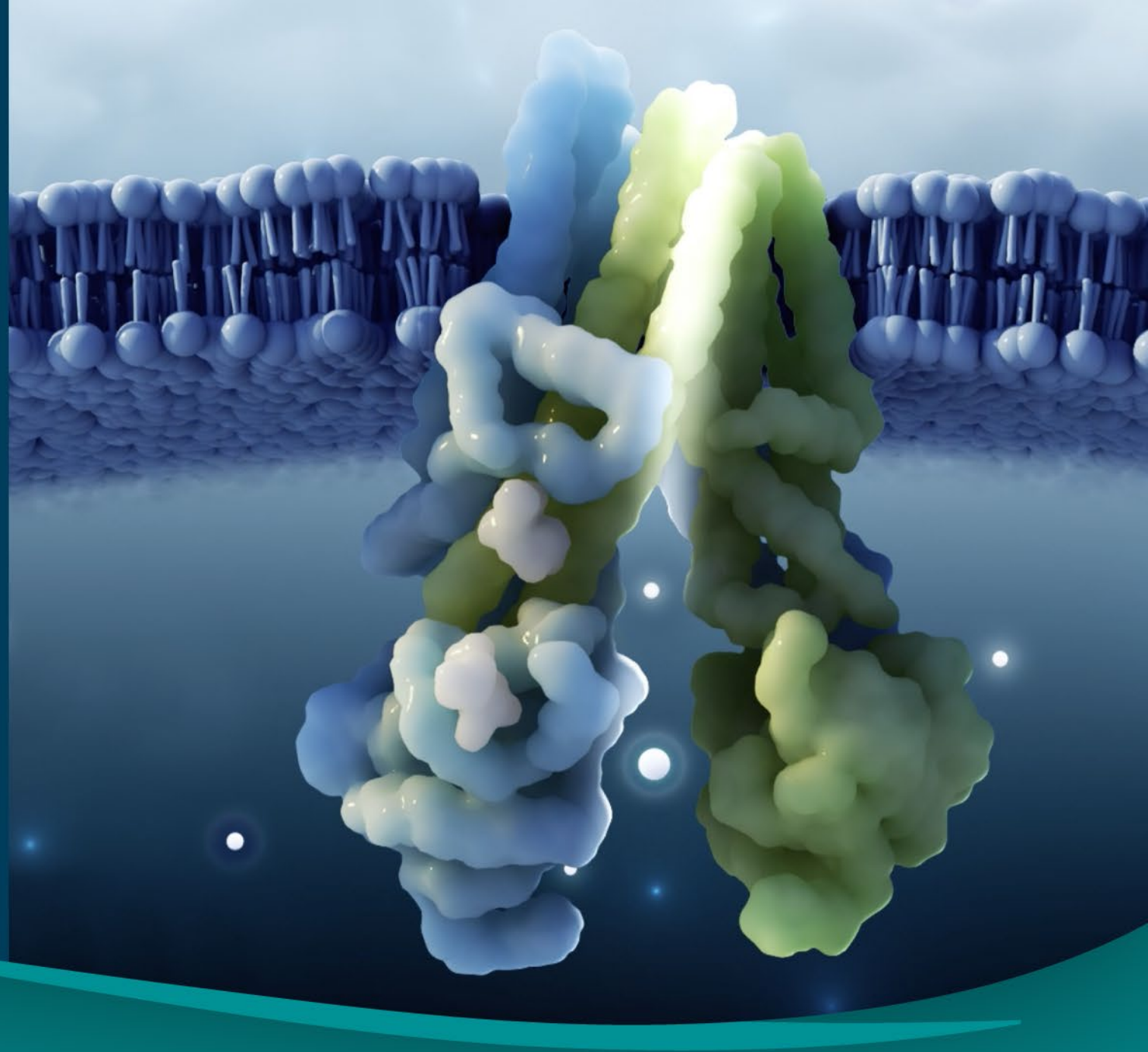
Sionna Therapeutics

Positive Phase 1 Data for NBD1 Stabilizers SION-719 & SION-451

June 4, 2025



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Sionna Overview &
Today's Announcement
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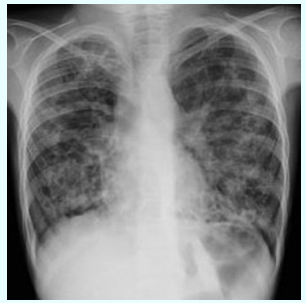
Sionna's novel approach focused on stabilizing NBD1 has the potential to revolutionize the current CF treatment paradigm

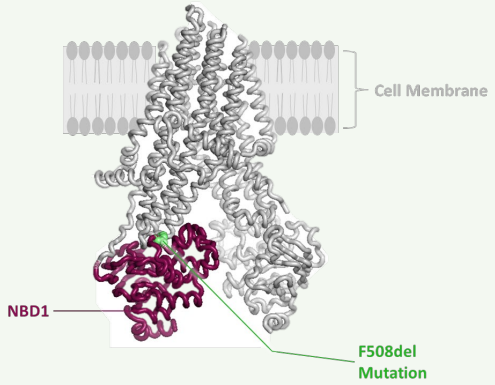
HIGH UNMET NEED IN LARGE MARKET



Despite current treatments, >2/3rd of patients do not have normal CFTR function

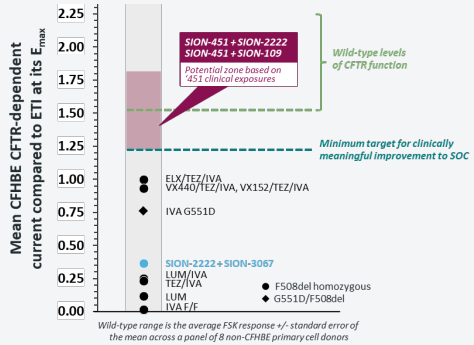
Today's market is >$11B[1], expected to be $15B by 2029[2]

NBD1, A CRITICAL CF TARGET



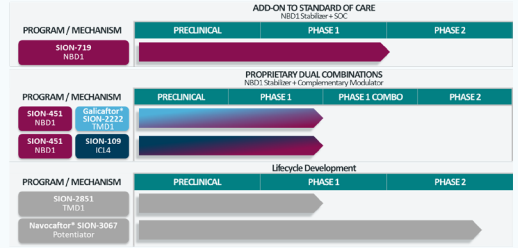
We believe NBD1 has the potential to deliver full CFTR function, and none of the approved CFTR modulators directly stabilize NBD1

PREDICTIVE ASSAY / BIOMARKERS*



Industry standard CFHBE assay and sweat chloride biomarker have been highly predictive of clinical outcomes for approved CFTR modulators

FRANCHISE DRIVES STRATEGIC OPTIONALITY



Robust clinical stage pipeline of NBD1 stabilizers and complementary modulators provides multiple potential paths to transform the standard of care for CF patients

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1. VRTX 4Q24 earnings call; 2. 2024 Wall Street research estimates; *Source: Preclinical assays conducted by Sionna; results observed from our preclinical studies may not necessarily be predictive of clinical outcomes, and actual outcomes may differ; CF – Cystic fibrosis; NBD1 - Nucleotide Binding Domain 1 of CFTR; CFTR - CF transmembrane conductance regulator; CFHBE – CF Human Bronchial Epithelial primary cells

We believe stabilizing NBD1 is central to unlocking meaningful improvements in clinical outcomes for CF patients

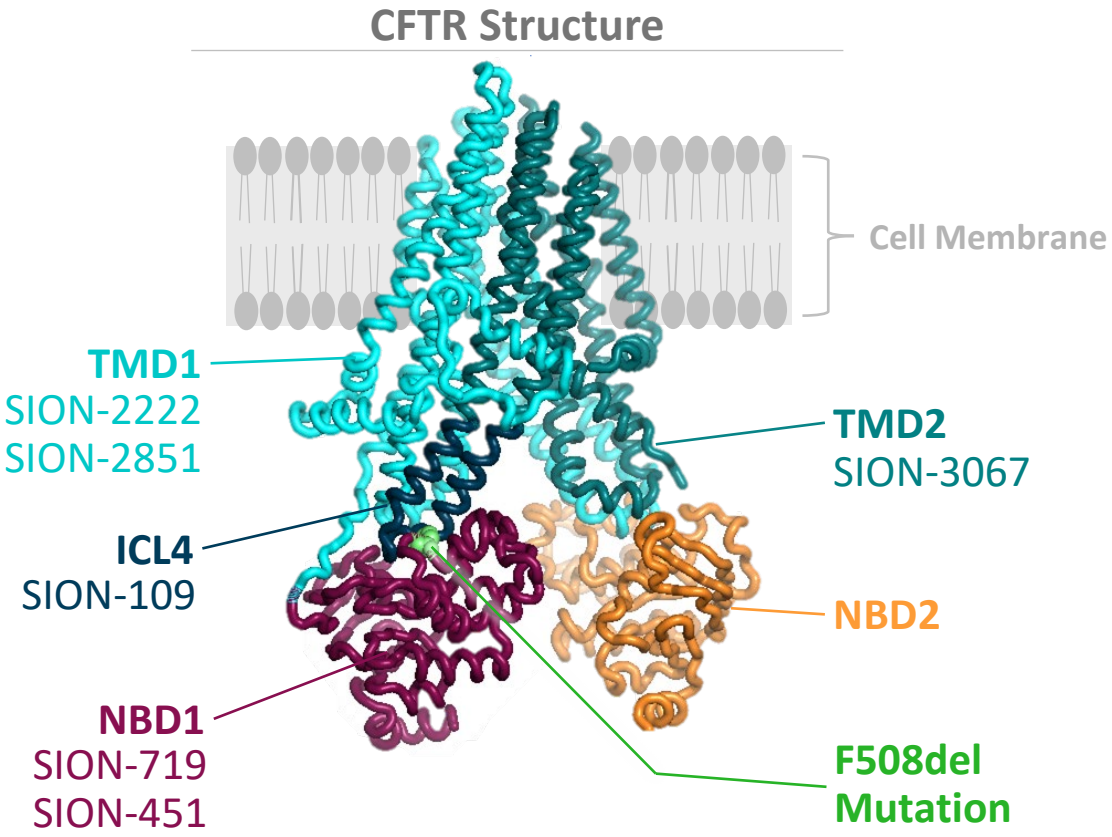
The Importance of NBD1

~90% of people with CF have a F508del mutation; **F508del resides within the NBD1 domain of CFTR**

F508del severely destabilizes CFTR, preventing its normal folding, trafficking, and function

None of the approved CFTR modulators directly stabilize NBD1

We believe stabilizing NBD1 is the key to normalizing CFTR function



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

Highlights from today's announcement

Positive NBD1 Phase 1 Results

- ✓ Both NBD1 stabilizers SION-719 and SION-451 exceeded our desired PK targets, were generally well-tolerated, and will be advanced to the next phases of development

NBD1 Portfolio Strategy

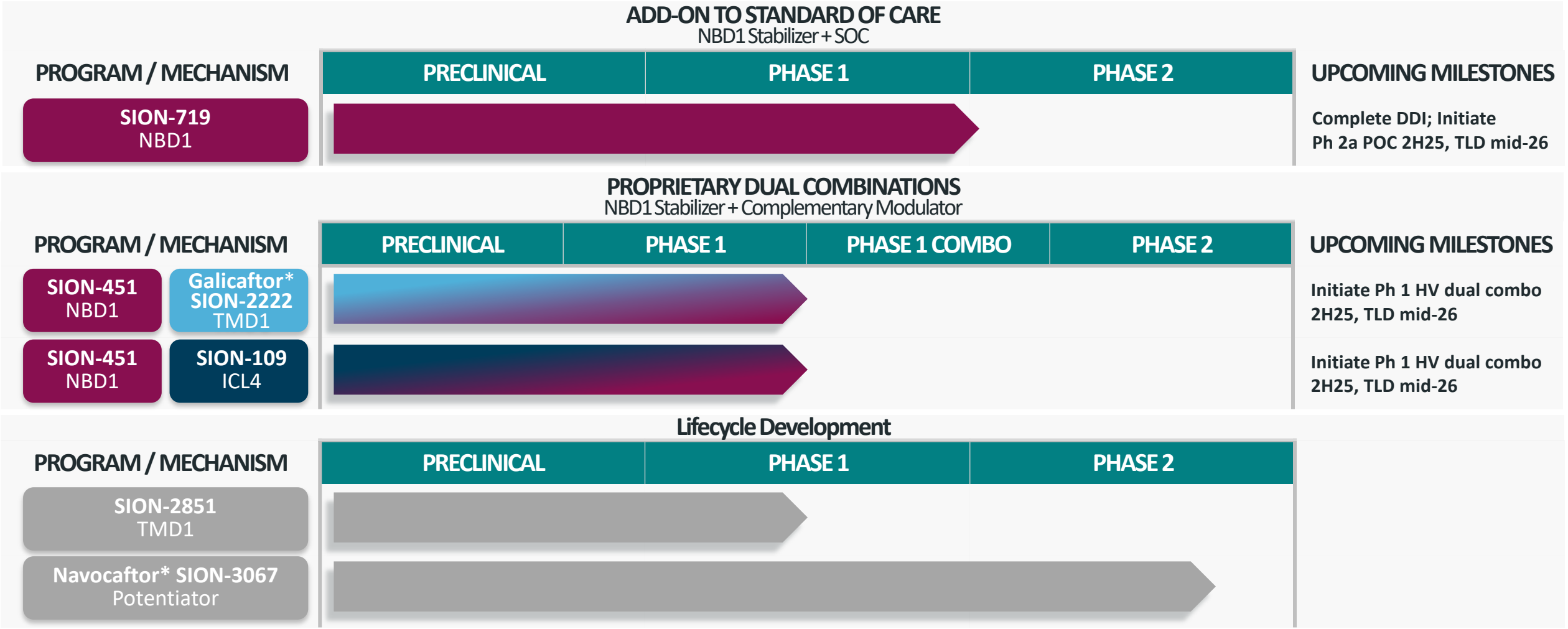
- ✓ **SION-719** to advance as add-on to SOC in Phase 2a proof-of-concept trial, based on high potency at low doses
- ✓ **SION-451** to advance as anchor in proprietary dual combinations, based on higher exposure achieved

Next Development Phase

- ✓ **SION-719** IND cleared and DDI study ongoing; Phase 2a proof-of-concept in CF patients to be initiated 2H25
- ✓ **SION-451** Phase 1 healthy volunteer dual combination trial to be initiated 2H25
- ✓ Well-positioned to execute with **cash runway into 2028**

IND – Investigational New Drug; DDI – Drug to drug interaction; PK – pharmacokinetic
SOC – standard of care

Sionna has a robust and differentiated pipeline, with several near-term clinical milestones



*Licensed compounds from AbbVie; Clinical trials conducted by AbbVie; Galicaftor and Navocaftor completed Ph 2 combination trials
POC – proof of concept; HV – healthy volunteer; TLD – topline data; Ph – phase

NBD1 Programs Phase 1 Data:

SION-719 & SION-451

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SION-719 and SION-451: Phase 1 trial summary

Phase 1 clinical trials of SION-451 and SION-719

- Evaluating the safety, tolerability, and PK profiles of single and multiple ascending doses of SION-719 and SION-451 in healthy volunteers
- 3:1 randomized, double-blind, placebo-controlled studies in Australia
- SAD/MAD parts dosed as oral suspension (fasted unless noted); MAD dosing duration of 10 days
- FE/BE Part C evaluated the effect of food on PK and bioequivalence of a tablet formulation compared to oral suspension

SION-719

- 100 total subjects dosed:
  - SAD: 20mg (fasted & fed), 40mg, 80mg, 160mg
  - MAD (BID): 20mg, 40mg, 80mg, 120mg, 160mg
  - FE/BE Part C: doses in add-on to SOC and dual combo ranges

SION-451

- 110 total subjects dosed:
  - SAD: 25mg (fed), 75mg (fasted & fed), 150mg, 300mg, 450mg
  - MAD (BID): 25mg (fed), 75mg, 150mg, 225mg, 300mg
  - FE/BE Part C: doses in add-on to SOC and dual combo ranges

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SAD – single ascending dose; MAD – multiple ascending dose;
FE – Food Effect; BE – BioEquivalence; BID – twice a day

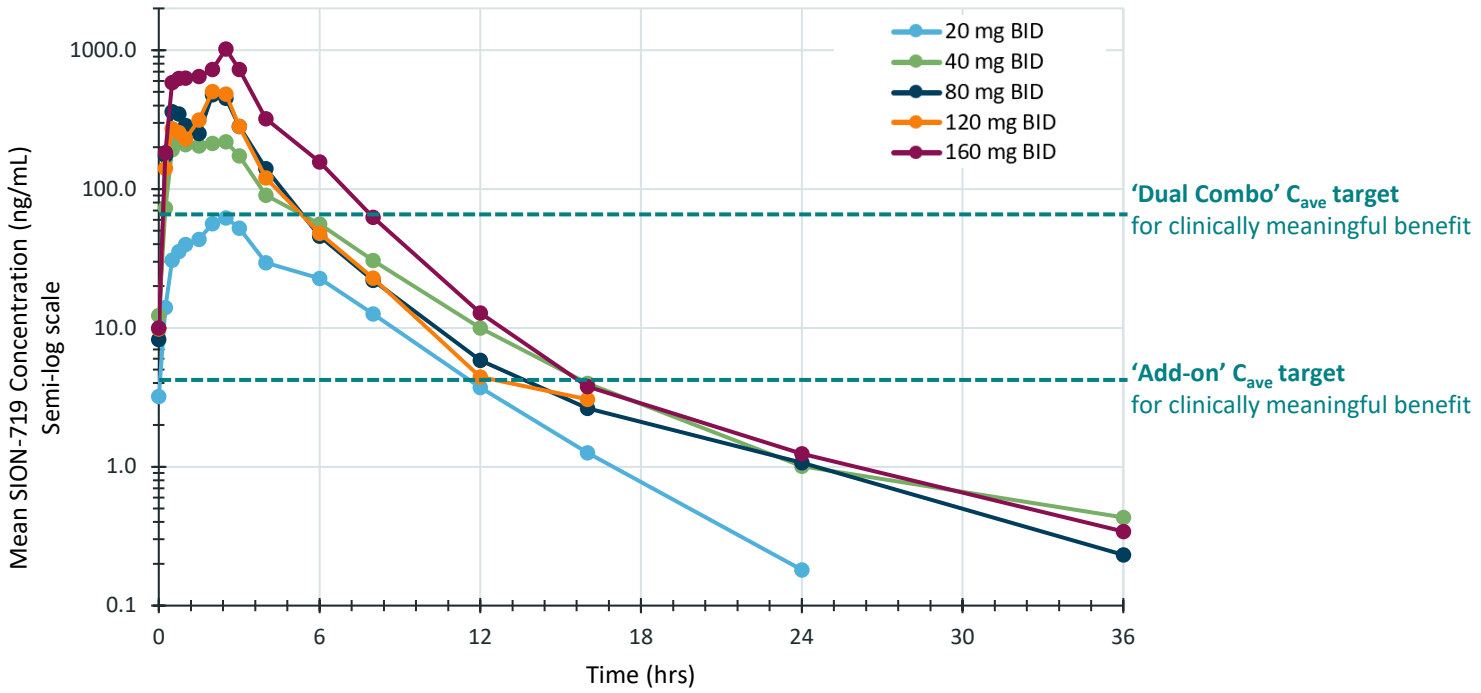
SION-719 exceeded target exposures predicted by our CFHBE assay, and is an attractive add-on to SOC given high potency at lower doses

Add-on target coverage at all doses studied; dual combination coverage at ≥40mg BID

High potency and synergy with SOC support lower dose SION-719 for Phase 2a POC trial

Part C data support use of the tablet in future studies and indicate SION-719 can be dosed in fed or fasted state

MAD PK Summary Day 10 Through 36 Hours Post-administration



Each solid line shows mean concentration data from a dosing cohort on Day 10

PK observations in the SAD portion of the trial were generally consistent with the MAD findings shown

SION-719 Phase 1 data suggest favorable tolerability profile

SION-719 MAD Safety Summary

Study Participants (n)*	Placebo BID (n=10)	20 mg BID (n=6)	40 mg BID (n=6)	80 mg BID (n=6)	120 mg BID (n=6)	160 mg BID (n=6)	MAD Total (n=40)
Any TEAE, n (%)	**4 (40)**	**2 (33)**	**4 (67)**	**6 (100)**	**5 (83)**	**3 (50)**	**24 (60)**
Mild (Grade 1)	3 (30)	2 (33)	3 (50)	5 (83)	2 (33)	3 (50)	18 (45)
Moderate (Grade 2)	1 (10)	-	2 (33)	1 (17)	3 (50)	1 (17)	8 (20)
Severe (Grade 3)	-	-	-	-	-	-	-
Life-threatening (Grade 4)	-	-	-	-	-	-	-
Leading to treatment discontinuation	-	-	-	-	-	-	-
Serious TEAEs, n (%)	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Most frequent TEAEs (≥2 subjects), n (%)							
Headache	-	-	4 (67)	1 (17)	2 (33)	2 (33)	9 (23)
Diarrhea	1 (10)	1 (17)	-	-	-	2 (33)	4 (10)
Nausea	1 (10)	-	1 (17)	-	-	1 (17)	3 (8)
Catheter site phlebitis	-	-	-	-	2 (33)	-	2 (5)
Pruritus	1 (10)	-	-	-	-	1 (17)	2 (5)

SION-719 SAD, MAD, and FE/BE Safety Highlights

- No SAEs; Most TEAEs were mild to moderate (Grade 1 or Grade 2)
- No TEAEs led to discontinuation of drug and no dose-limiting TEAEs observed
- No TEAEs related to LFTs in treated subjects
- No clinically meaningful trends in other safety parameters, vital signs or ECG parameters

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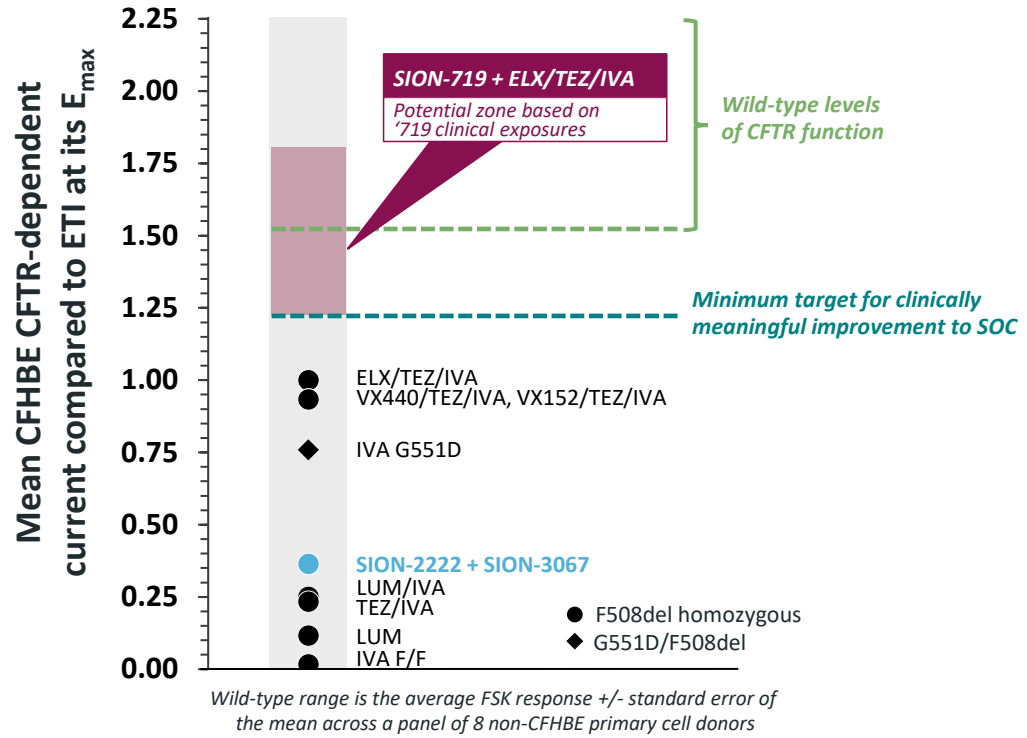
* Safety Population; includes participants who received all or part of at least 1 dose of SION-719 or placebo
SAE – Serious adverse event; TEAE – Treatment emergent adverse event after first dose of drug; LFT – liver function test
ECG – electrocardiogram

SION-719's potency at low doses enables a potentially differentiated profile when added to SOC

Potential of SION-719 as an add-on to SOC*



Phase 1 PK data indicate potential for **clinically meaningful benefit, including to wild-type levels, as add-on to SOC** based on CFHBE target zone

Minimum CFHBE target represents at least 10 mmol/L SwCl and ~3 $ppFEV_1$ improvement

*Source: Preclinical assays conducted by Sionna and SION-719 Phase 1 PK; results observed from our preclinical studies may not necessarily be predictive of clinical outcomes, and actual outcomes may differ

Gating mutation – G551D CFTR; ELX – elexacaftor; IVA – ivacaftor; LUM – lumacaftor; TEZ – tezacaftor; Trikafta – ELX/TEZ/IVA; SwCl – Sweat Chloride; ppFEV - Percent Predicted Forced Expiratory Volume

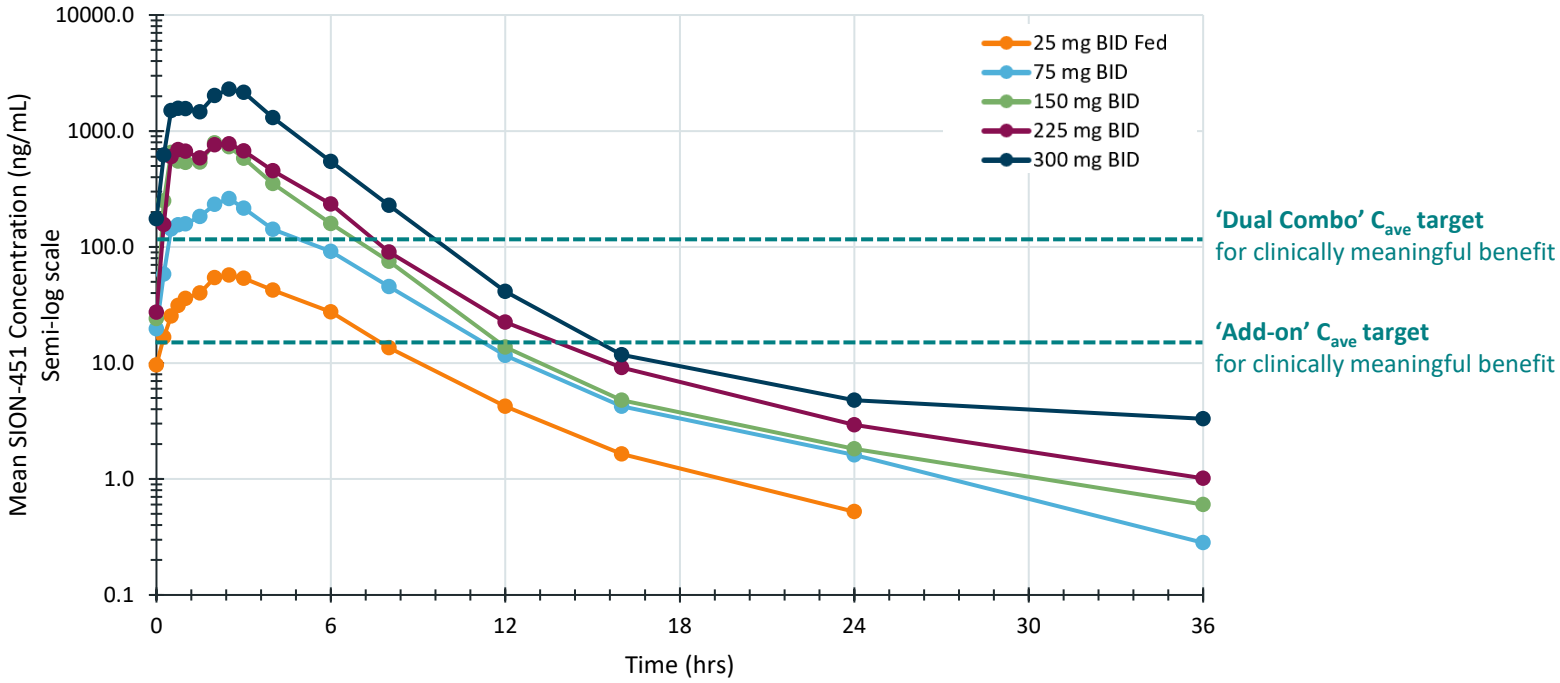
SION-451 is an ideal anchor for dual combinations given level of exposures achieved in target concentration zones as predicted by our CFHBE assay

Dual combination target coverage at ≥75 mg BID; add-on target coverage at all doses studied

High exposures support evaluating SION-451 upper dose range in Ph 1 HV dual combination

Part C data support use of the tablet in future studies and indicate SION-451 can be dosed in fed or fasted state

MAD PK Summary Day 10 Through 36 Hours Post-administration



Each solid line shows mean concentration data from a dosing cohort on Day 10

PK observations in the SAD portion of the trial were generally consistent with the MAD findings shown

SION-451 Phase 1 data suggests favorable tolerability profile

SION-451 MAD Safety Summary

Study Participants (n)*	Placebo BID (n=9)	25 mg BID (n=6)	75 mg BID (n=5)	150 mg BID (n=6)	225 mg BID (n=6)	300 mg BID (n=6)	MAD Total (n=38)
Any TEAE, n (%)	**5 (56)**	**2 (33)**	**3 (60)**	**3 (50)**	**4 (67)**	**2 (33)**	**19 (50)**
Mild (Grade 1)	4 (44)	2 (33)	2 (40)	1 (17)	4 (67)	-	13 (34)
Moderate (Grade 2)	1 (11)	-	1 (20)	1 (17)	-	2 (33)	5 (13)
Severe (Grade 3)	-	-	-	1 (17)	-	-	1 (3)
Life-threatening (Grade 4)	-	-	-	-	-	-	-
Leading to treatment discontinuation	-	-	-	-	-	-	-
Serious TEAEs, n (%)	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Most frequent TEAEs (≥2 subjects), n (%)							
Headache	3 (33)	1 (17)	-	-	2 (33)	1 (17)	7 (18)
Influenza	-	-	-	2 (33)	-	-	2 (5)
Upper Respiratory Tract Infection	1 (11)	-	-	1 (17)	-	-	2 (5)

SION-451 SAD, MAD, and FE/BE Safety Highlights

- No SAEs; Most TEAEs were mild to moderate (Grade 1 or Grade 2)
- No TEAEs led to discontinuation of drug and no dose-limiting TEAEs observed
- 1 Grade 1 TEAE related to LFTs observed in a treated subject who tested positive for influenza[1]; no TEAEs related to LFTs in other cohorts
  - Same subject had transient Grade 3 neutropenia at same time as influenza
- No clinically meaningful trends in other safety parameters, vital signs or ECG parameters

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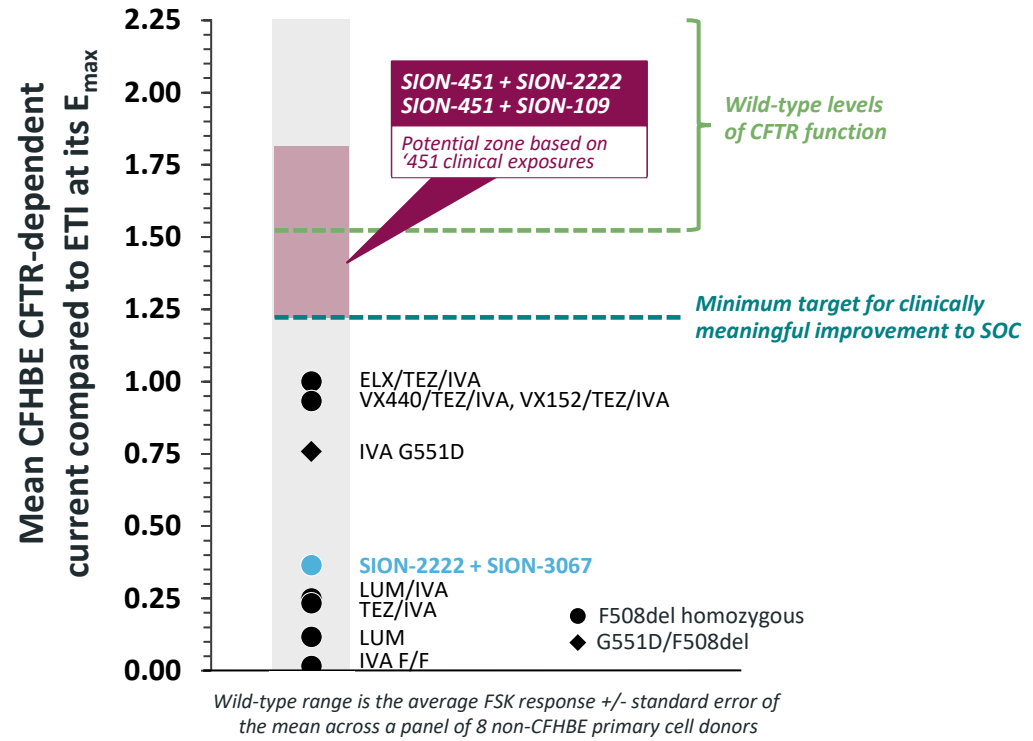
* Safety Population; includes participants who received all or part of at least 1 dose of SION-451 or placebo
1. Subject was in isolated dose cohort of SION-451 (150mg BID) that was impacted by an outbreak of respiratory infection

SION-451 in a dual combination has the potential to provide a superior treatment option for people living with CF

Potential of SION-451 in dual combination*



Phase 1 PK data indicate potential for **clinically meaningful benefit, including to wild-type levels, in a dual combination** based on CFHBE target zone

Minimum CFHBE target represents at least 10 mmol/L SwCl and ~3 ppFEV$_1$ improvement

*Source: Preclinical assays conducted by Sionna and SION-451, SION-2222 and SION-109 Phase 1 PK; results observed from our preclinical studies may not necessarily be predictive of clinical outcomes, and actual outcomes may differ

Clinical Strategy

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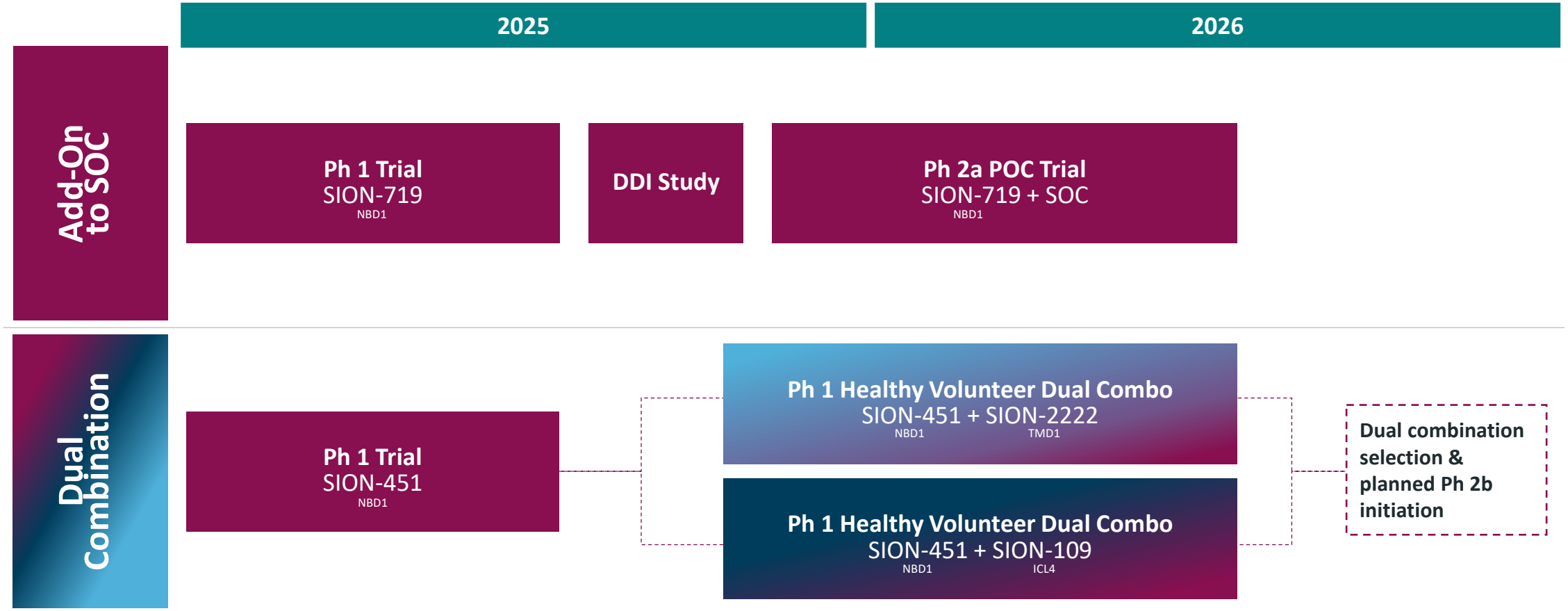
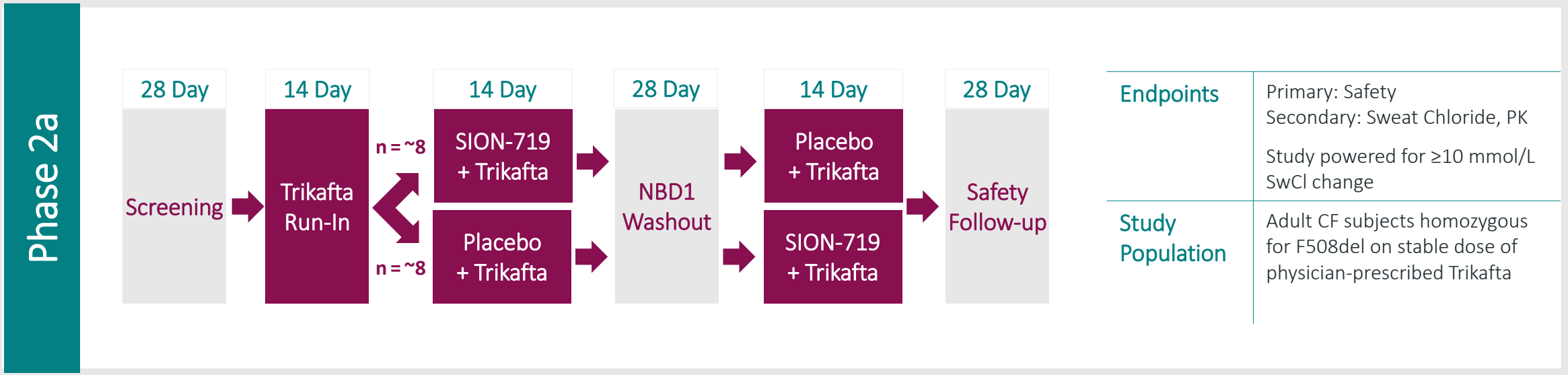
Sionna's development strategy is data-driven with multiple near-term milestones



Phase 2a Proof-of-Concept trial in patients with CF:
Evaluating low-dose SION-719 added to Trikafta®



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

Objectives are to demonstrate that
NBD1 is mechanistically unique from, and synergistic with the components of Trikafta, and that adding a low dose of NBD1 to Trikafta is associated with improved CFTR function

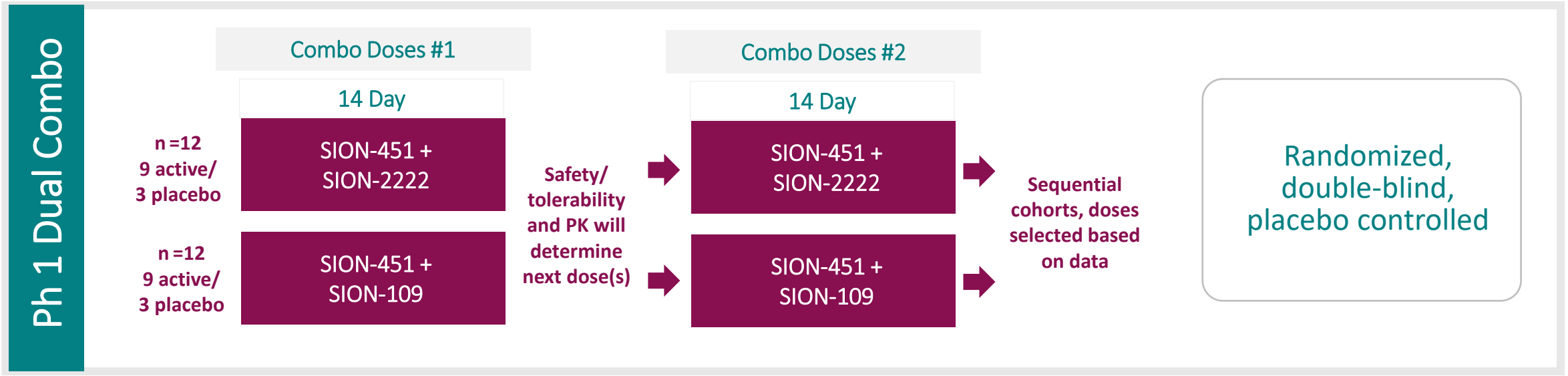
Clinical Drug-Drug Interaction (DDI) study in healthy subjects:
Evaluating the potential to dose SION-719 with standard dose Trikafta

Clinical Pharmacology

Midazolam is a sensitive CYP3A4 substrate, used as a probe to test the potential effect of SION-719 on CYP3A4 substrates (e.g., components of Trikafta)

Objective is to evaluate the potential effect of low dose SION-719 on CYP3A4 substrate to **confirm SION-719 can be combined with the standard dose of Trikafta**

Healthy volunteer Phase 1 dual combination trial:
Evaluating safety, tolerability, and PK of SION-451-based dual combos



Objective is to evaluate **different doses of SION-451 in combination with SION-2222 and with SION-109 in healthy volunteers** and **select the NBD1-based dual combination to advance to Phase 2b** trial in patients with CF

Unmet Need & Opportunity

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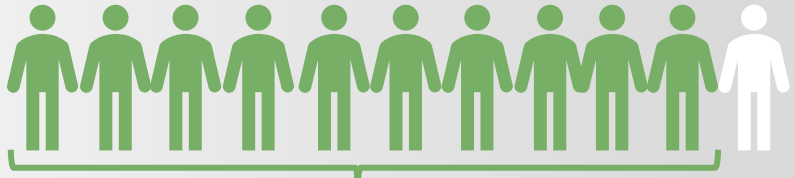
Significant commercial opportunity exists for our NBD1-led franchise to provide a potentially transformative treatment for CF, if approved

~106K patients with CF across 94 countries[1]

U.S.	EU4 + UK	ROW
~33k	~35k	~38k



~90% patients have at least one F508del-CFTR mutation[2]

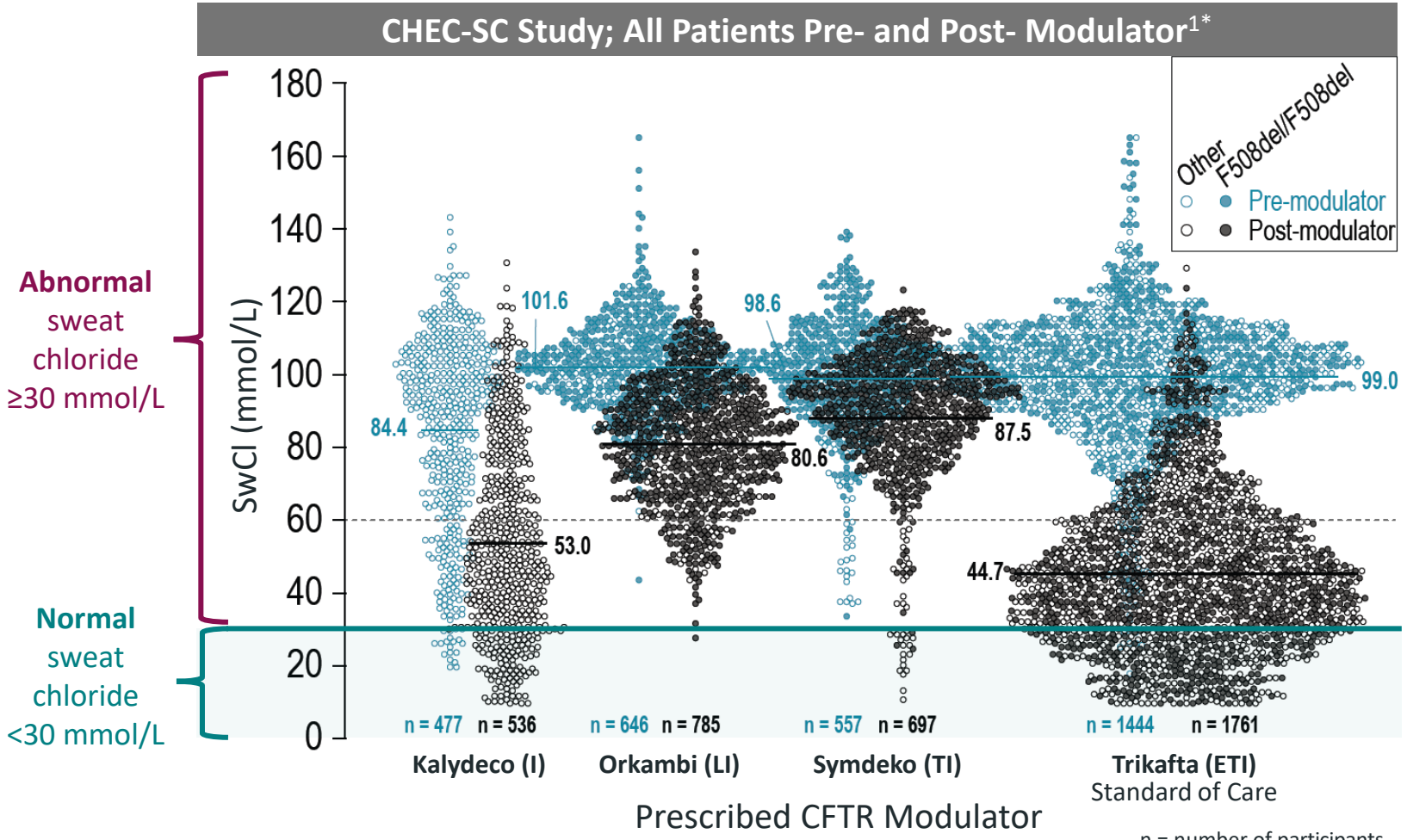
- **>2/3** of patients on SOC do not have normal CFTR function[3]*
- **>6,000** patients have discontinued use of approved CFTR modulators[4]
- **>20%** of eligible patients are currently **not on CFTR modulators**[5]
- Non-responders or patients with tolerability challenges have **limited or no alternatives**[6]

>$11B
worldwide revenues of CFTR modulators today[7]

$15B
opportunity by 2029[8]

1. CFF estimates 2023, 2023 CFF Registry data, 2022 ECFS Registry
2. Taylor-Cousar 2019; 3. Konstan, NACFC poster 2022
4. Vertex 2Q23 Earnings Call Transcript; 5. Vertex 2Q24 Earnings Presentation; 6. Sploletini 2022 JCF; Ibrahim 2023 Front Pharmacol
7. VRTX 4Q24 earnings call; 8. 2024 Wall Street research estimates; * as measured by sweat chloride
EU4 – FR, GE, IT, ES; ROW – Rest of World

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



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 <30mmol/L

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

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*

Closing

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We intend to transform the treatment of CF and are well-positioned given our deep portfolio, strong clinical execution, and cash runway into 2028

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$219M Upsized IPO in 1Q25 Funds Sionna into 2028

Pioneering a First-in-Class NBD1 Portfolio with Pipeline of Combination Assets

Proven Execution with Multiple Ph 1 Trials

Multiple Upcoming Clinical Milestones

Positive Ph 1 data support advancing both NBD1s while maintaining timelines and cash runway