Safety, Tolerability, and Pharmacokinetics of Novel NBD1 Stabilizers SION-719 and SION-451 from Two Phase 1 First-in-Human Studies

sionna™

Poster 107

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- Novel NBD1 stabilizers SION-719 and SION-451 were generally safe and well tolerated in healthy volunteers
- Both compounds exceeded concentrations that, based on the CFHBE assay, have the potential to deliver clinically meaningful benefit over standard-of-care modulators as combination therapies with complementary modulators

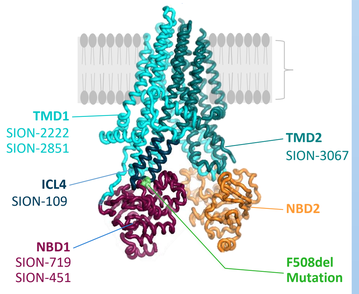
Background and Rationale

Unmet Need in Cystic Fibrosis

- Despite treatment advances, unmet need remains high in people with CF
- Greater than 2/3 of pwCF on current triple-combination modulator therapies do not have normal CFTR function, as measured by sweat chloride < 30 mmol/L [1,2,3]

Novel NBD1 Stabilizers Aim to Address Central Driver of CFTR Dysfunction

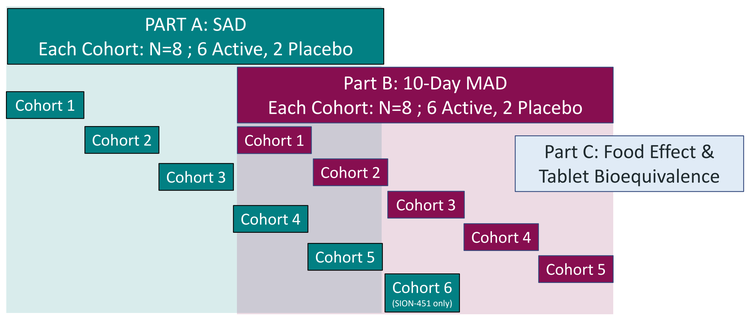
- Nucleotide-binding domain 1 (NBD1) of the CFTR protein plays a key role in the folding, stability, trafficking, and function of CFTR
- F508del defect resides within the NBD1 domain, and severely destabilizes NBD1, preventing normal CFTR folding, domain assembly, trafficking, half-life, and function
- Sionna NBD1 stabilizers represent a novel and differentiated mechanism. When combined with other modulators that improve domain-domain assembly, NBD1 stabilizers have the potential to fully correct F508del-CFTR function[4]



Methods

- Two studies evaluated the safety, tolerability, and PK profiles of single (SAD) and multiple ascending doses (MAD) of SION-719 and SION-451 in healthy volunteers
- Both studies were randomized, double-blind, and placebo-controlled
- In SAD/MAD parts of each study, study drug was dosed as oral suspension
- MAD dosing duration of 10 days
- Both studies also evaluated the effect of food on PK and bioequivalence (FE/BE) of a tablet formulation compared to oral suspension
- SION-719: 100 total participants dosed with SION-719 or placebo
  - SAD: 20mg (fasted & fed), 40mg, 80mg, 160mg
  - MAD (BID): 20mg, 40mg, 80mg, 120mg, 160mg
  - FE/BE: doses studied in ranges to support add-on to standard of care (SOC) modulators and dual combination
- SION-451: 110 total participants dosed with SION-451 or placebo
  - SAD: 25mg (fed), 75mg (fasted & fed), 150mg, 300mg, 450mg
  - MAD (BID): 25mg (fed), 75mg, 150mg, 225mg, 300mg
  - FE/BE: doses studied in ranges to support add-on to SOC modulators and dual combination

Figure 1. SION-719 and SION-451: SAD, MAD, and FE/BE Study Design



SION-719 Safety and Tolerability

- SAD and MAD had overall consistent safety profile
- No SAEs; all 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 increased liver enzymes in SION-719 treated participants
- No clinically meaningful trends in other safety parameters, vital signs, or ECG

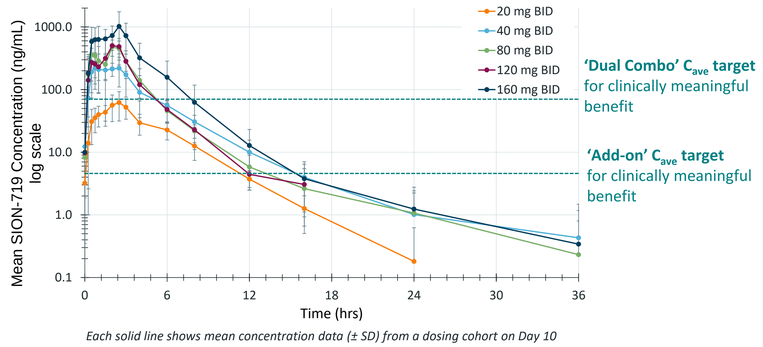
Table 1. TEAEs in SION-719 10-day MAD Cohorts

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 participants), 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 Pharmacokinetics

- Add-on target coverage at all doses studied; dual combo coverage at ≥40 mg BID
- High potency and synergy with SOC modulators support lower dose SION-719 for Phase 2a Proof-of-Concept (POC) trial ('Add-on')
- FE/BE data support use of the tablet in future studies and indicate SION-719 can be dosed in fed or fasted state

Figure 2. SION-719 Steady-State MAD PK: Day 10 Through 36 Hours Post-Administration



Each solid line shows mean concentration data (± SD) from a dosing cohort on Day 10

SION-451 Safety and Tolerability

- SAD and MAD had overall consistent safety profile
- 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
- One Grade 1 TEAE related to liver enzymes observed in a treated participant who tested positive for influenza; no TEAEs related to liver enzymes in other cohorts
  - Same participant had transient Grade 3 neutropenia at time of influenza
- No clinically meaningful trends in other safety parameters, vital signs, or ECG

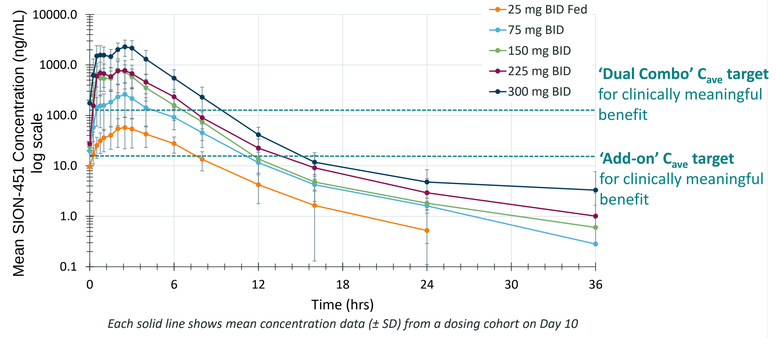
Table 2. TEAEs in SION-451 10-day MAD Cohorts

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 participants), 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 Pharmacokinetics

- Dual combo coverage at ≥75mg BID; Add-on target coverage at all doses studied
- High exposures support evaluating SION-451 upper dose range in Phase 1 healthy volunteer dual combination ('Dual Combo')
- FE/BE data support use of the tablet in future studies and indicate SION-451 can be dosed in fed or fasted state

Figure 3. SION-451 Steady-State MAD PK: Day 10 Through 36 Hours Post-Administration



Each solid line shows mean concentration data (± SD) from a dosing cohort on Day 10

Conclusions

- Novel NBD1 stabilizers SION-719 and SION-451 were generally safe and well tolerated in healthy volunteers in these Phase 1 studies.
- Both compounds exceeded concentrations that, based on the CFHBE assay, have the potential to deliver clinically meaningful benefit when:
  - SION-719 is added to existing standard-of-care modulators
  - SION-451 is used in a novel dual combination with one of Sionna's complementary modulators
- SION-719 and SION-451 can be dosed fed or fasted based on FE/BE cohorts
- Novel NBD1s are advancing in two studies in 2025 with read-outs expected in 2026: Phase 2a POC with SION-719 and Phase 1 dual combination study with SION-451

References

1. Konstan et al., Abstract #43. NACFC 2022
2. Zemanick et al., JCF 2024 Jul 1;23(4):676–84.
3. Keating et al. Lancet Resp Med. 2025 Mar 1;13(3):256–71.
4. Hurlbut et al. Abstract WS19.01. ECFS 2025

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Abbreviations: BID: twice daily; CFHBE Assay: Cystic Fibrosis Human Bronchial Epithelial Cell Assay; FE/BE: food effect / bioequivalence; ICL4: fourth intracellular loop; NBD: nucleotide-binding domain; PK: Pharmacokinetics; POC: proof-of-concept; pwCF: people with CF; SOC: standard-of-care; TEAE: treatment-emergent adverse event; TMD: transmembrane domain

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