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Clinical Stage CFTR NBD1 Stabilizers SION-719 and SION-451 Synergize with Galicaftor (SION-2222) or SION-109 to Enable Full Correction of ΔF508-CFTR

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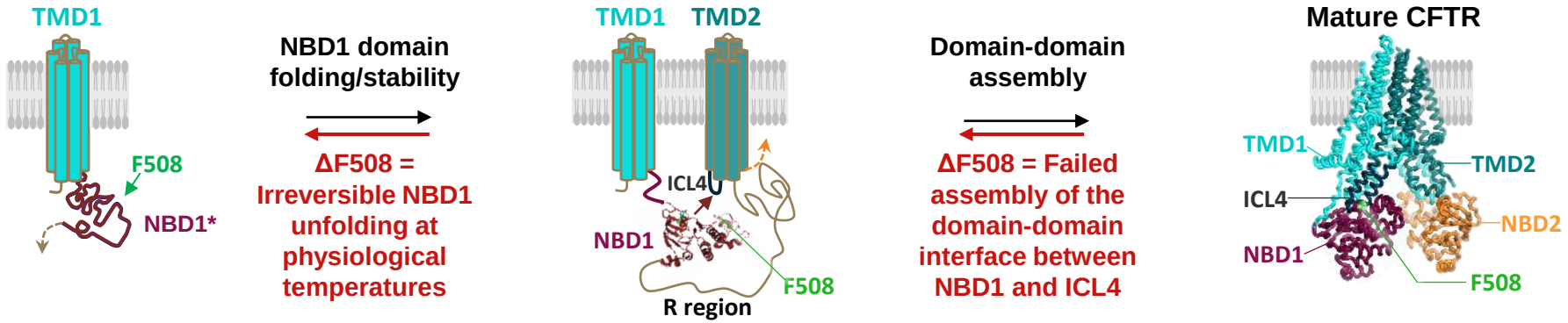
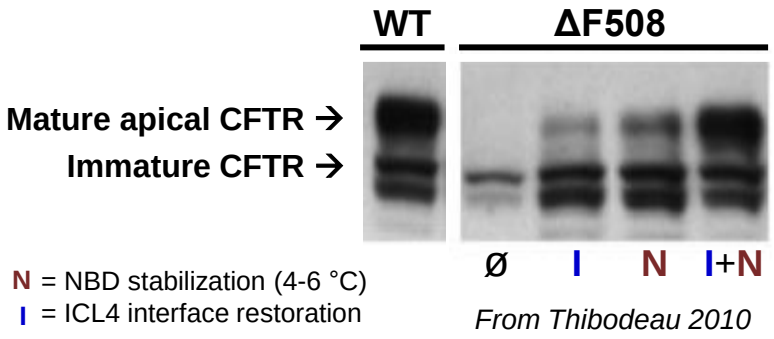
Disclosure - a shareholder and employee of Sionna Therapeutics

NBD1 Instability and Defective CFTR Domain-Domain Assembly are Central Drivers of ΔF508-CFTR Dysfunction

ΔF508-CFTR's critical NBD1 instability and domain assembly errors must be addressed for full correction



Proof of Hypothesis: Stabilizing NBD1 with Second-Site Mutations



N = NBD stabilization (4-6 °C)
I = ICL4 interface restoration

From Thibodeau 2010

CFTR suppressor mutations that stabilize NBD1 and the NBD1-ICL4 interface fully restore ΔF508-CFTR maturation and function to wild type (WT) levels, this may provide a potential roadmap to more effective future therapies.

Thibodeau *et al*. J Biol Chem. 2010 Nov 12;285(46):35825-35.

*NBD1 = Nucleotide Binding Domain 1, TMD = Transmembrane Domain, ICL4 = Intracellular Loop 4

With the Goal of Fully Normalizing ΔF508-CFTR, Sionna is Developing Novel Drugs that Address Key Drivers of Dysfunction

- **Leveraging over a decade of investment by Sionna, CFF, Genzyme and Sanofi, we've had unique success in directly targeting NBD1, a mechanism previously deemed undruggable†**
  - >10 screening campaigns (biophysical, cell-based and virtual) covering >2 million compounds
  - ~150 X-ray co-structures were solved to guide structure-based optimization of NBD1 stabilizers
  - >5,000 compounds across different NBD1 ligand series were designed, synthesized and assessed
- **NBD1 stabilizers SION-719 and SION-451 have completed Phase 1 trials**
  - Additional NBD1 development candidates identified
- **Sionna is also advancing complementary modulators that are synergistic with NBD1:**
  - SION-2222 (galicaftor) – a Phase 2 stage TMD1-directed corrector, with demonstrated clinical activity.
  - Sionna's ICL4-directed SION-109 – an ICL4-directed corrector with a completed Phase 1 trial.
- **Our vision is to develop novel NBD1-led proprietary dual combinations with mechanistically complementary modulators to provide clinically meaningful benefit to CF patients**

Hypothesis: Stabilize NBD1 + Improve Domain Assembly = Potential for Full CFTR correction

† Hall J, et al. Protein Sci 2016; 25(2):360-373.

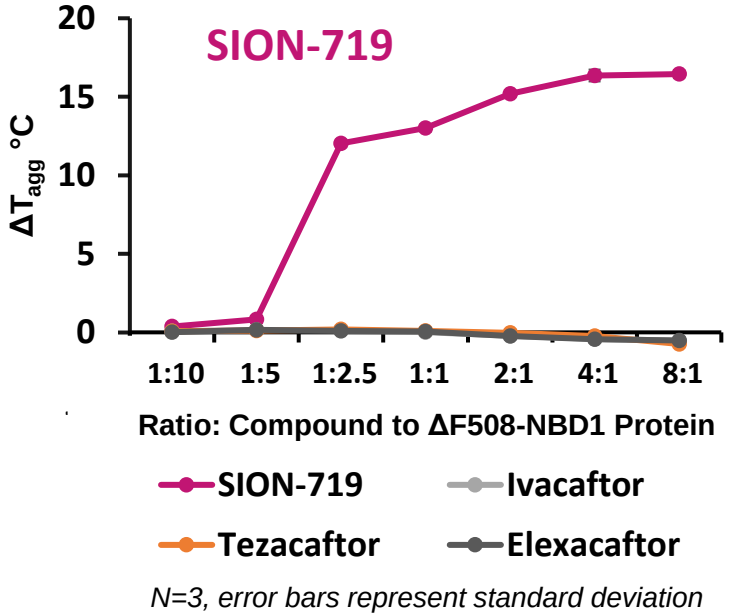
Sionna NBD1 Stabilizers SION-719 and SION-451 Bind to and Stabilize the NBD1 Domain of CFTR

Surface Plasmon Resonance

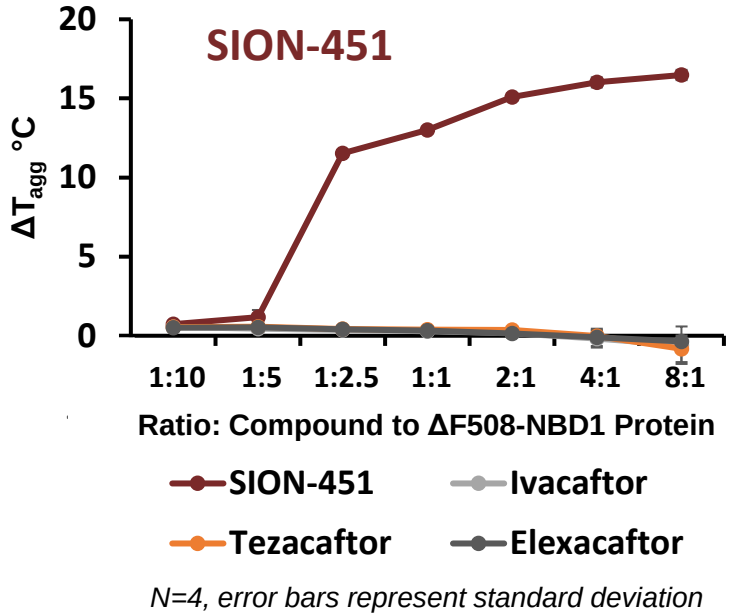
	NBD1 Affinity
Compound	ΔF508-NBD1 K_D (μM)
SION-719	0.0043
SION-451	0.0024
ELX	No binding observed
TEZ	No binding observed
IVA	No binding observed

SION-719 and SION-451 display high affinity 1:1 NBD1 binding

Differential Static Light Scattering



N=3, error bars represent standard deviation



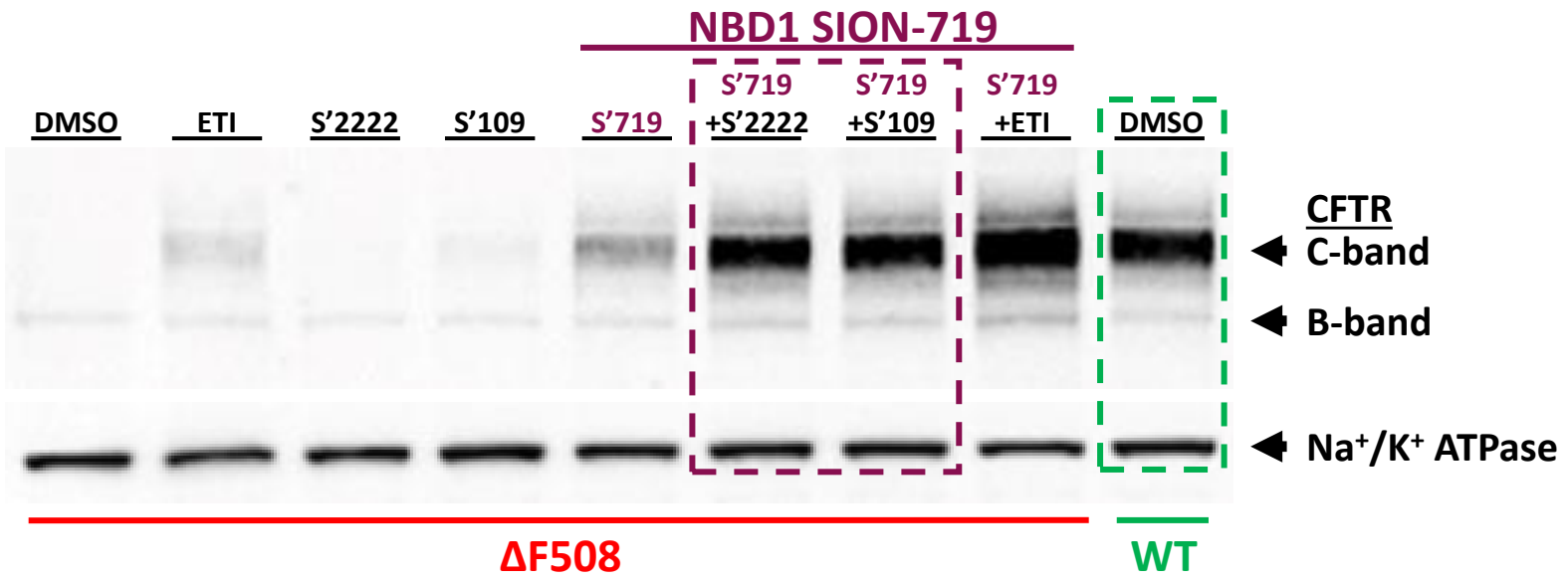
N=4, error bars represent standard deviation

SION-719 and SION-451 can increase the stability of isolated ΔF508-NBD1 by 16°C

High-resolution X-ray crystal co-structures were solved for >150 Sionna NBD1 stabilizers, clearly demonstrating direct interaction

NBD1 Stabilizer SION-719 Corrects ΔF508-CFTR Maturation to WT Levels when Combined with SION-2222 or SION-109

Western blot WT and ΔF508-CFTR in CFSMEo-



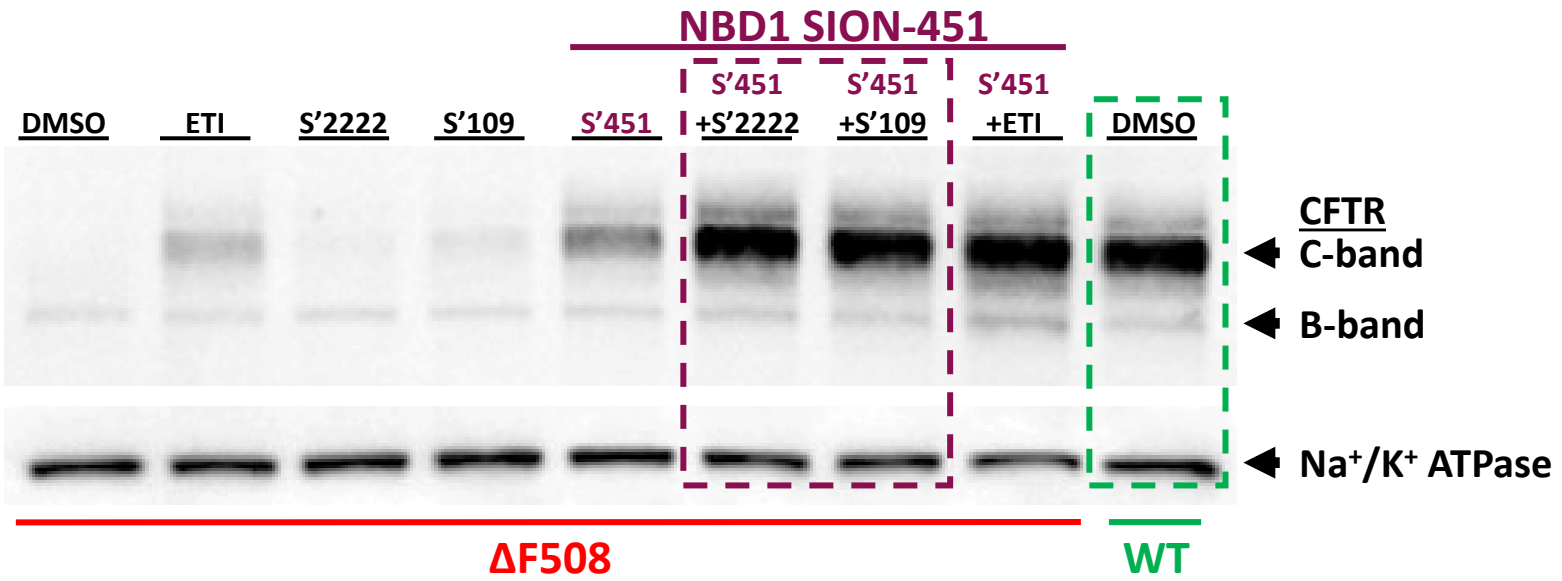
ETI at E_{max}
- ELX (10μM) – approved ICL4 Corrector
- TEZ (5μM) – approved TMD1 Corrector
- IVA (0.1μM) – approved Potentiator

SION-719 (1.5μM) – Sionna NBD1 Stabilizer
SION-109 (3μM) – Sionna ICL4 Corrector
SION-2222 (5μM) – Sionna TMD1 Corrector

Hypothesis:* *Stabilize NBD1* + *Improve Domain Assembly* = *Potential for Full CFTR correction

NBD1 Stabilizer SION-451 Corrects ΔF508-CFTR Maturation to WT Levels when Combined with SION-2222 or SION-109

Western blot WT and ΔF508-CFTR in CFSMEo-



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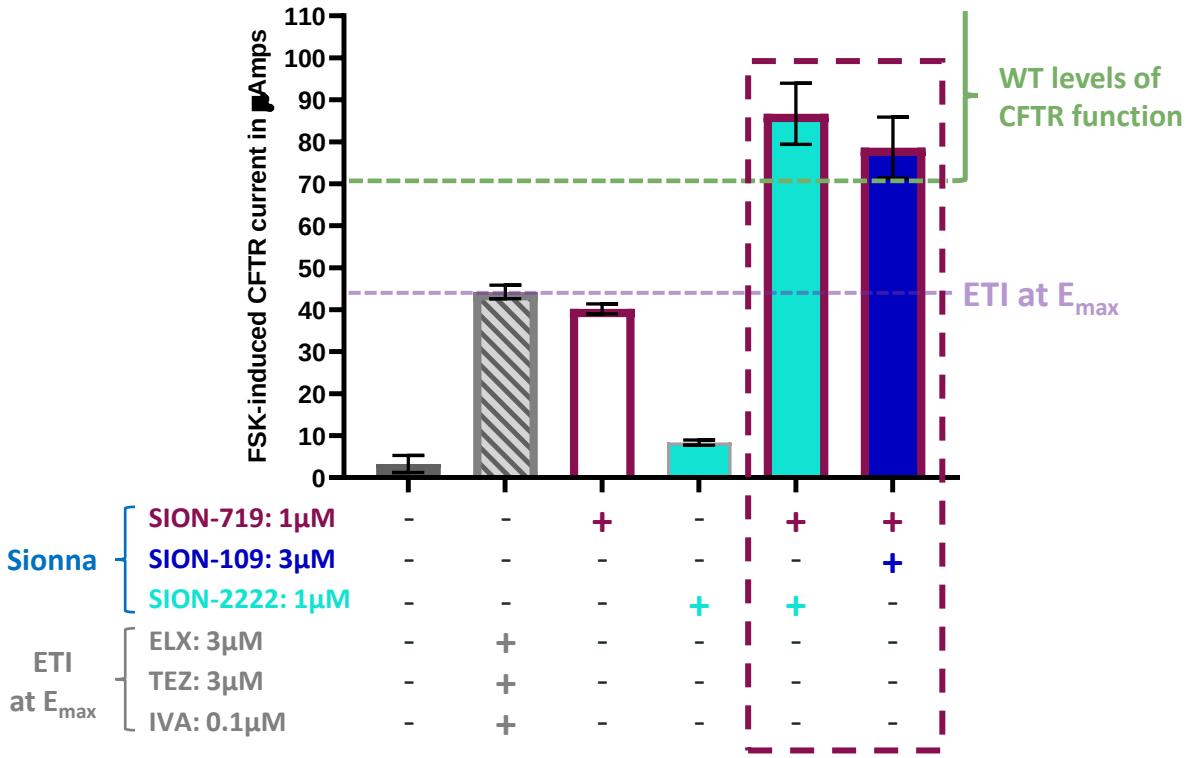
NBD1 Dual Combos with SION-109 or SION-2222 can Correct ΔF508-CFTR Function to WT Levels in CFHBEs at E_{max}

CFHBE VALI (E_{max} Concentrations)



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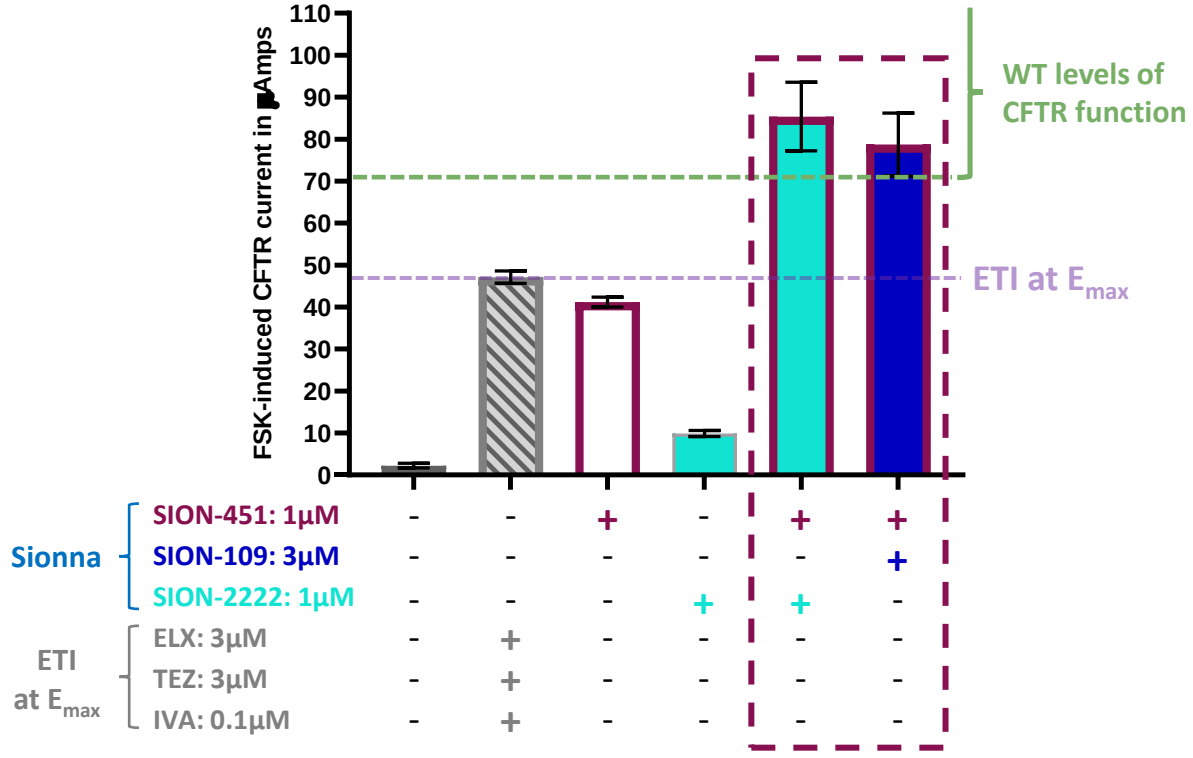
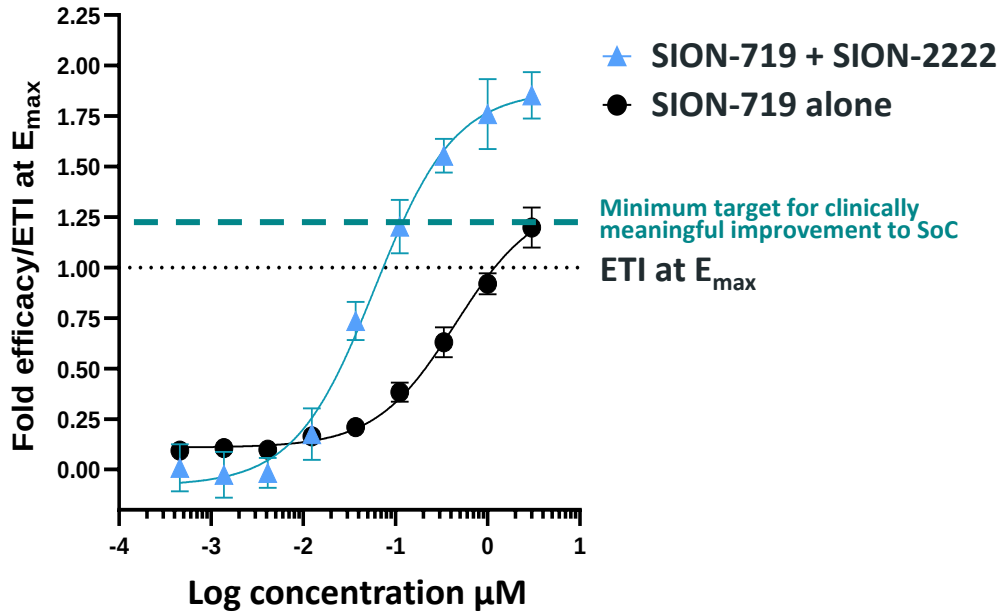
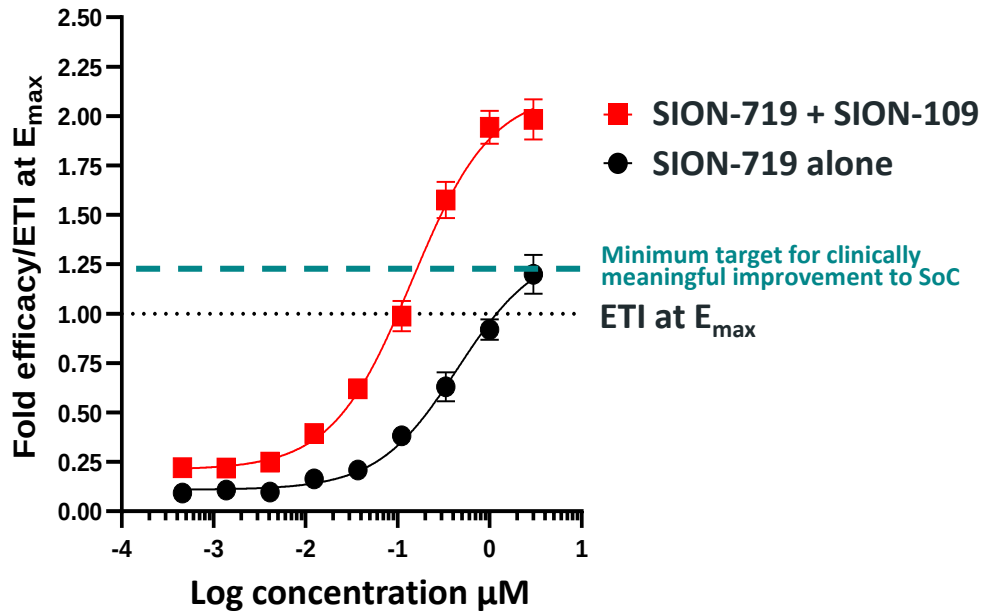


Hypothesis: Stabilize NBD1 + Improve Domain Assembly = Potential for Full CFTR correction

SION-719 Dual Combos Show Potential for Clinically Meaningful Benefit at Concentrations Below E_{max}

Dose Response in *ΔF508/ΔF508* CFHBE + Human Serum (20% v/v)
Translation Model





ETI at E_{max} = 3µM ELX, 45µM,TEZ, 0.3µM IVA

SION-719, when combined with SION-2222 (galicaftor) or SION-109 at concentrations below its E_{max}, corrects CFTR function in the preclinical model to levels we expect will provide clinically meaningful benefit to pwCF with the ΔF508-CFTR mutation

SoC = Standard of Care

SION-451 Dual Combos Show Potential for Clinically Meaningful Benefit at Concentrations Below E_{max}

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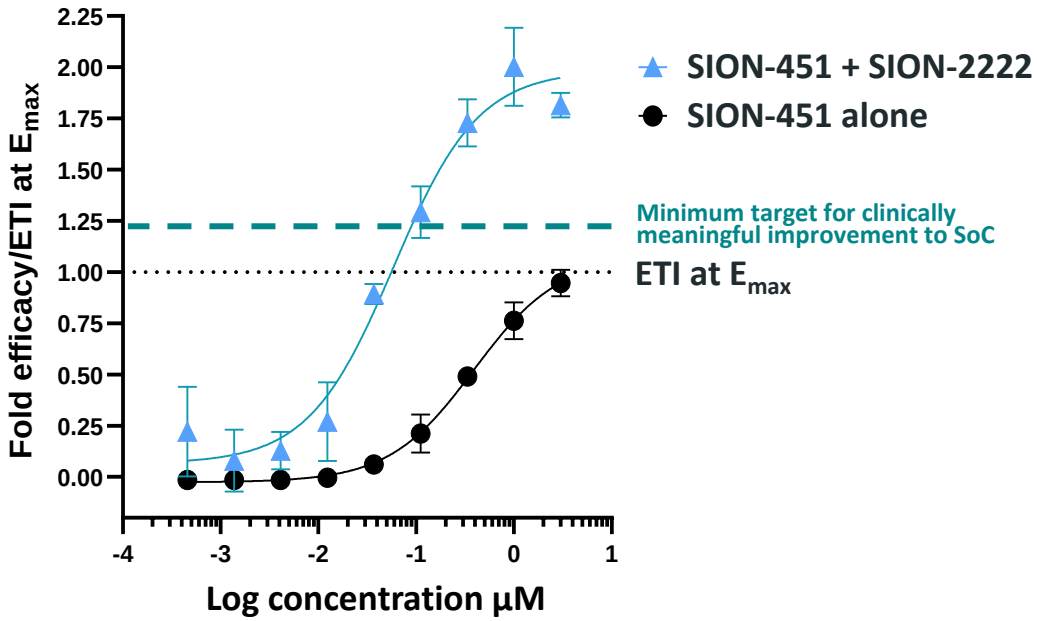

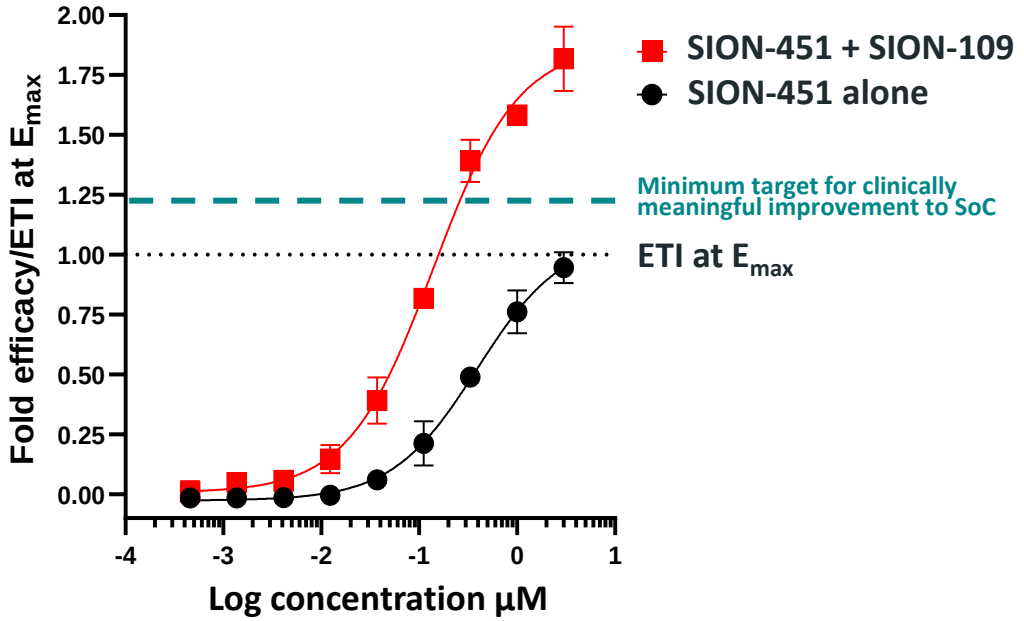

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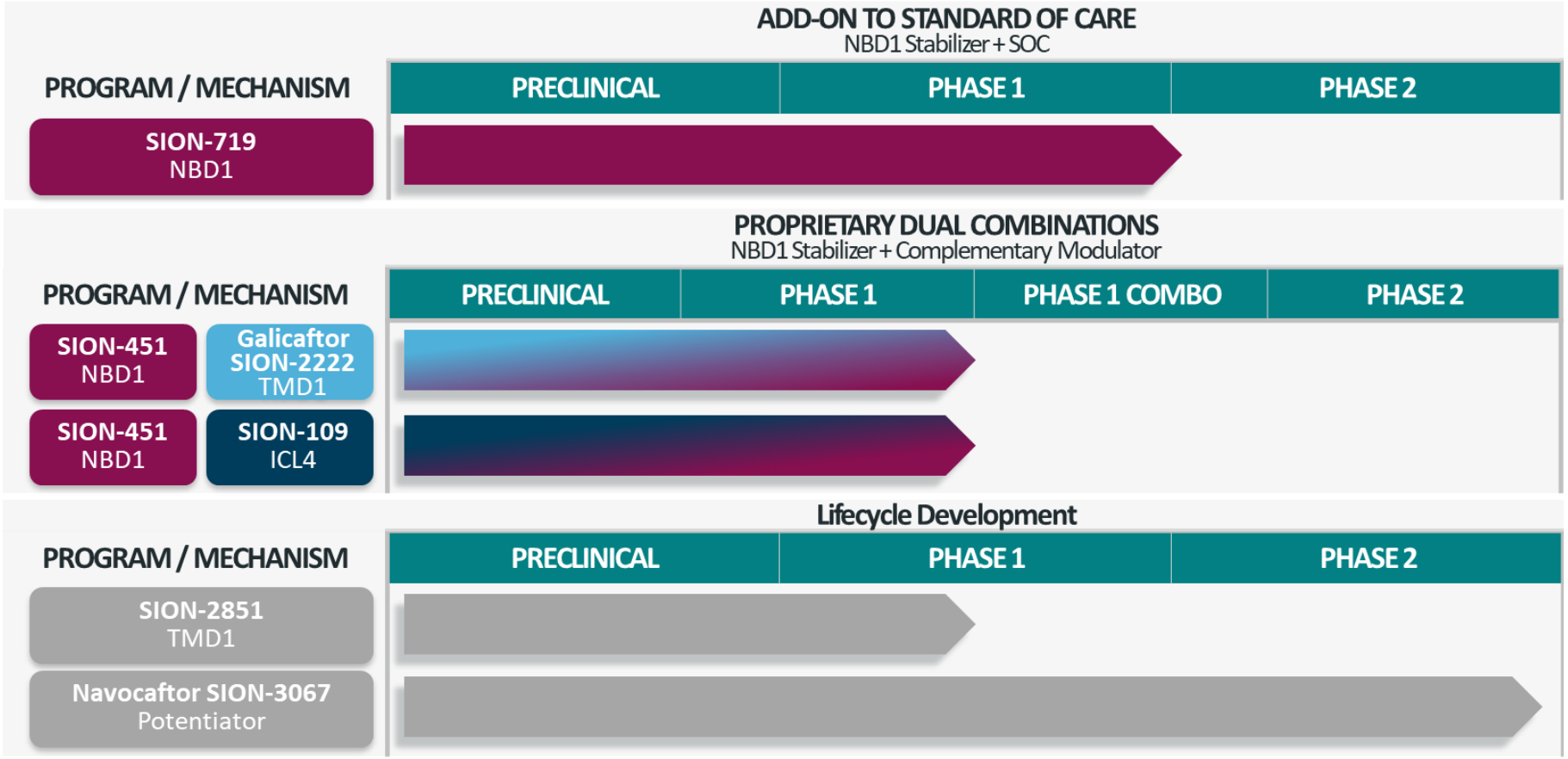
Anchored by NBD1, Sionna's Goal is to Deliver Differentiated and Highly Effective New Medicines for pwCF



Sionna is advancing a portfolio of NBD1 stabilizers and complementary CFTR correctors with a goal to enable more patients to achieve normal CFTR function