**Abstract**

Background: Cystic Fibrosis (CF) results from CFTR mutations, the most prevalent being ΔF508. CFTR Modulator Combinations Complex ΔF508-CFTR NBD1 Stability Defect and Enable Full CFTR Correction. Autocrine signaling is a key driver of impaired folding, trafficking, maturation, and function of ΔF508-CFTR. Thus, the ability to correct ΔF508-CFTR measures a potential advantage for development. Restoring ΔF508-CFTR function to WT levels during clinical development holds potential to extend current ΔF508-CFTR therapies. However, ΔF508-CFTR’s molecular biogenesis is dominated by NBD1, which is considered undruggable.

**Sionna’s NBD1 stabilizers, including SION-638 in phase 1, can restore WT function to ΔF508-CFTR.**

**Introduction**

ΔF508-CFTR leads to NBD1 instability and defective CFTR domain-domain assembly. NBD1 destabilization is a key driver of impaired ΔF508-CFTR folding, trafficking, and function, and to WT levels when combined with mechanistically complimentary agents. Data from the clinically predictive CFHBE model suggest that NBD1 stabilizes enable multiple potential paths to full restoration of CFTR function for most CF patients.

**Sionna 638 Stabilizes the NBD1 Domain of CFTR**

![Figure 1](image1.png)

**Figure 1. Surface Plasmon Resonance (SPR) was used to evaluate SION-638 binding to human WT NBD1 (SION-451 and SION-638) and ΔF508-NBD1 isoforms. SION-638 demonstrated 1:1 binding across all NBD1 isoforms with WT values ranging from 10-fold in multiple experiments. Representative SPR sensorgrams and dose-response curves are shown.**

**Sionna 638 binders were assayed for NBD1 small molecule ligands by protein-observed NMR and high-resolution NBD1 X-ray crystal co-structures were solved for ~150 compounds.**

**Sionna 638 Stabilizes the NBD1 Domain of CFTR**

![Figure 2](image2.png)

**Figure 2. SION-638 increases the thermal stability of WT NBD1 and ΔF508-NBD1. SION-638 treated ΔF508-NBD1 has greater stability than that of untreated WT-NBD1.**

**Sionna 638 Stabilizes the NBD1 Domain of CFTR**

![Figure 3](image3.png)

**Figure 3. SION-638 increases the thermal stability of ΔF508-NBD1 in all tested conditions.**

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![Figure 4](image4.png)

**Figure 4. Western blot demonstrating that SION-638 corrects ΔF508-CFTR to WT levels when used in combination with complementary modulators. NBD1-ICL4 interface (vlc-TEZ) is restored to WT levels when combined with NBD1-directed correctors, or the combination thereof.**

**Sionna 638 Improves ΔF508-CFTR Maturation**

![Figure 5](image5.png)

**Figure 5. Impact of Sionna high potency NBD1 development candidate SION-719 and ΔF508 stabilizers in Phase 1 of ΔF508-CFTR maturation. Western blots of ΔF508-CFTR expressing CFHBE cells. Biological replicates comparing both ΔF508-CFTR and WT-CFTR expressing cells treated as indicated.**

**Sionna 638 Improves ΔF508-CFTR Trafficking**

![Figure 6](image6.png)

**Figure 6. Impact of Sionna high potency NBD1 development candidate SION-719 and ΔF508 stabilizers in Phase 1 of ΔF508-CFTR trafficking. Western blots of ΔF508-CFTR expressing CFHBE cells. Biological replicates comparing both ΔF508-CFTR and WT-CFTR expressing cells treated as indicated.**

**Sionna 638 Increases ΔF508-CFTR Function**

![Figure 7](image7.png)

**Figure 7. ΔF508-CFTR responses were measured as a percentage of WT-CFTR.**

**References**

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