



Sionna Therapeutics Announces Plans to Advance SION-451 + SION-2222 Dual Combination into Phase 2a Proof-of-Concept Trial

September 14, 2026

Post hoc analyses of SION-719 PreciSION CF subset showed a mean placebo-adjusted sweat chloride reduction of up to -8.6 mmol/L consistent with NBD1 biological activity

Dual combination Phase 2a trial expected to initiate in first quarter of 2027

46% workforce reduction and other cost-saving measures prioritize advancing the dual combination program and extend cash runway into the second half of 2029

Sionna to host conference call today at 4:30 p.m. ET

WALTHAM, Mass., Sept. 14, 2026 (GLOBE NEWSWIRE) -- Sionna Therapeutics, Inc. (Nasdaq: SION), a clinical-stage biopharmaceutical company on a mission to develop novel medicines for cystic fibrosis (CF), today announced plans to advance SION-451 + SION-2222, its preferred proprietary dual combination, into the AscenSION CF Phase 2a proof-of-concept (POC) trial, and results from the company's post hoc analysis of the PreciSION CF Phase 2a trial. The decision to advance SION-451 + SION-2222 follows an extensive review of clinical, pharmacokinetic (PK) and nonclinical data from PreciSION CF. Learnings from that trial and the previous Phase 1 dual combination trial will inform the development strategy for the dual combination.

"It was important for us to take the time to complete a comprehensive post hoc data analysis to better understand the SION-719 PreciSION CF trial results and their potential implications before determining the right path forward for our dual combination," said Mike Cloonan, President and Chief Executive Officer of Sionna. "The analysis identified important factors that we believe complicated interpretation of the trial and may have blunted the impact of NBD1 stabilization. The post hoc findings, together with the favorable Phase 1 results for SION-451 + SION-2222, support advancing the dual combination into Phase 2a. We have been inspired by the CF community, whose voices continue to reinforce the need for new treatment options."

"Despite the substantial progress made, there remains a significant need for new options for people with CF," said Gregory S. Sawicki, M.D., M.P.H., Director of the Cystic Fibrosis Center at Boston Children's Hospital and Associate Professor of Pediatrics at Harvard Medical School. "Directly stabilizing NBD1 continues to represent a differentiated approach to addressing the underlying biology of CF. I'm excited to see Sionna proceed with a Phase 2a trial of SION-451 + SION-2222, which will be an important next step in further exploring whether the NBD1 biology can translate into meaningful benefit for people with CF."

Post Hoc Analysis of SION-719 PreciSION CF Phase 2a Clinical Trial

PreciSION CF Phase 2a ([NCT07108153](#)) was a randomized, double-blind, placebo-controlled, crossover trial that evaluated the safety and tolerability of SION-719 when added to Trikafta® in 15 adult participants with CF homozygous for F508del. Change in sweat chloride, an important measure of CFTR function, was the key activity endpoint. As previously [announced](#), the trial did not achieve its key activity endpoint, and Sionna is not advancing SION-719 as an add-on to SOC.

Following the announcement of topline results, Sionna conducted a comprehensive analysis of the clinical, PK, and nonclinical data to better understand the PreciSION CF outcome, including implications for the NBD1 mechanism and the SION-451 + SION-2222 dual combination.

The primary analysis in the trial assessed placebo-adjusted sweat chloride change using Day 1 as baseline. A prespecified secondary analysis assessed placebo-adjusted sweat chloride change using the baseline measured at the start of each treatment period. Across the 14 evaluable participants, results were similar under both methodologies, with placebo-adjusted sweat chloride changes of -1.0 mmol/L in the primary analysis and -1.1 mmol/L in the secondary analysis.

The post hoc analysis identified three factors that may have confounded the observed treatment effect:

- **PK outliers:** Three participants had drug exposures (one with SION-719 and two with the components of Trikafta (elexacaftor/tezacaftor/ivacaftor; ETI) at key timepoints consistent with non-adherence. Excluding these confounded participants resulted in mean placebo-adjusted sweat chloride change of -8.6 mmol/L using the secondary analysis of baseline measured at the start of each treatment period. The Company believes the secondary analysis to assess sweat chloride best accounts for variability observed between treatment periods.
- **Trikafta Exposure Levels:** ETI exposures were lower during SION-719 treatment periods, with mean exposures of all three components declining by approximately 25-30% on average while remaining relatively stable during placebo periods.
- **CFTR Channel Biology:** Post hoc analysis of preclinical CFHBE assay data suggests that the interaction between an NBD1 stabilizer, like SION-719, and a potentiator, like ivacaftor, may have blunted the additional benefit of NBD1 stabilization. This interaction is not observed when an NBD1 stabilizer is combined with complementary correctors targeting TMD1 or ICL4.

Sionna believes these analyses suggest that SION-719 was biologically active in the trial, but that PK outliers and complex interactions between SION-719 and Trikafta may have affected the observed outcome and blunted a potential treatment signal.

SION-451 + SION-2222 Dual Combination Phase 2 Development Plan

Sionna plans to advance SION-451 + SION-2222 into the AscenSION CF Phase 2a POC trial. The Company continues to believe that directly stabilizing NBD1 in combination with a complementary CFTR modulator has the potential to meaningfully improve CFTR function.

The AscenSION CF POC will be an open-label trial evaluating adults with CF homozygous for F508del treated with SION-451 + SION-2222 for 28 days. Participants will switch from Trikafta to SION-451 + SION-2222, and the trial will assess sweat chloride, safety, and PK. The design will incorporate key learnings from PreciSION CF with respect to dosing adherence and sweat chloride variability, and the trial is expected to initiate in the first quarter of 2027.

The decision to advance SION-451 + SION-2222 is supported by results from the Phase 1 healthy volunteer trial of SION-451-based dual combinations, for which the Company [announced](#) topline results on August 10, 2026. The trial achieved its safety, tolerability, and PK objectives. SION-451 + SION-2222 was identified as the preferred dual combination based on target exposure coverage, and the go-forward SION-451 twice daily (BID) + SION-2222 once daily (QD) regimen demonstrated a favorable tolerability profile. Phase 1 exposures of the planned doses were within the range associated with meaningful improvement in CFTR function in Sionna's CFHBE assay.

Corporate Update

Following the completion of a comprehensive review of its operations, Sionna's Board of Directors has approved a workforce reduction of approximately 46% and the Company has implemented other cost-saving measures to focus its resources on advancing SION-451 + SION-2222 and extend its operating runway. Sionna expects to retain the core clinical, scientific, regulatory, technical, and corporate capabilities required to advance the dual combination program. The Company currently estimates it will incur aggregate restructuring and related charges of approximately \$6.4 million.

Sionna ended Q2 2026 with approximately \$268.3 million in cash, cash equivalents, and marketable securities. The Company estimates that the workforce reduction, discontinuation of investment in SION-719 as an add-on to standard of care, and other cost-saving measures will extend its cash runway into the second half of 2029.

Webcast Details

Sionna Therapeutics' live webcast will begin at 4:30 p.m. ET today, September 14th, 2026, and can be accessed via this [link](#). Participants who prefer to listen via telephone, or ask a question, may register on Sionna's Investor Relations website or by clicking [here](#). A replay will be available on the "Events" page in the "Investors" section of Sionna's website at <https://investors.sionnatx.com/news-events/events>.

About Sionna Therapeutics

Sionna Therapeutics is a clinical-stage biopharmaceutical company on a mission to revolutionize the current treatment paradigm for cystic fibrosis (CF) by developing novel medicines that normalize the function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Sionna's goal is to deliver differentiated medicines for people living with CF that can restore their CFTR function to as close to normal as possible by directly stabilizing CFTR's nucleotide binding domain 1 (NBD1), which Sionna believes is central to potentially unlocking meaningful improvements in clinical outcomes and quality of life for people with CF. For more information about Sionna, visit www.sionnatx.com.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements about Sionna's beliefs and expectations regarding: its goal of transforming the treatment paradigm for CF; its interpretation of the results of the PreciSION CF trial and the impact of potential confounding factors on the interpretation of those results; the potential for NBD1 stabilization to improve CFTR function and produce clinical benefit, including beliefs about biological activity of SION-719 in PreciSION CF and the translatability of preclinical and in vitro assay data to clinical outcomes; the objectives, design, timing, initiation and conduct of a planned Phase 2a proof-of-concept trial of SION-451 + SION-2222; the therapeutic potential, clinical benefits and safety of SION-451 + SION-2222; the expected timing, scope, costs and benefits of the workforce reduction and other cost-saving measures; the Company's ability to retain the capabilities and personnel needed to advance SION-451 + SION-2222 and operate as a public company; the Company's expected cash runway; and other statements that are not historical facts.

In some cases, forward-looking statements can be identified by terms such as "may," "will," "should," "would," "expect," "plan," "anticipate," "could," "intend," "target," "project," "believe," "estimate," "predict," "potential" or "continue," or the negative of these terms or other similar expressions. Any forward-looking statements are based on management's current expectations and beliefs and are subject to risks, uncertainties and important factors that may cause actual events or results to differ materially, including uncertainties inherent in developing product candidates; interpreting the PreciSION CF results and potential confounding factors; the inherent limitations of post hoc analyses, which are exploratory and may not reliably predict future outcomes; the risk that in vitro and preclinical data may not translate to clinical benefit; the risk that results observed with one compound may not be predictive of results with a different compound or combination; and designing and conducting the planned Phase 2a trial. Additional risks include the Company's ability to demonstrate that its candidates are safe and effective; obtain regulatory feedback or approvals; achieve anticipated restructuring savings and runway extension; retain key personnel and capabilities following the workforce reduction; secure sufficient funding; and respond to general economic, industry and market conditions. These risks and

uncertainties are described in “Risk Factors” in Sionna’s most recent Quarterly Report on Form 10-Q and subsequent filings with the Securities and Exchange Commission. The events and circumstances reflected in the forward-looking statements may not be achieved or occur. Any forward-looking statements represent Sionna’s views only as of today and should not be relied upon as representing its views as of any subsequent date. Sionna disclaims any obligation to update any forward-looking statements except as required by law. No representations or warranties, express or implied, are made about the accuracy of any such forward-looking statements.

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