**HCR 564: Module 6 - Group Project Submission**

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## Background

Cystic Fibrosis (CF) is a genetic disorder affecting the respiratory and digestive systems, caused by mutations in the CFTR gene. This results in thick, sticky mucus that blocks airways, damages the lungs, and increases infection risk. Additionally, the thick mucus restricts the pancreas, hindering the movement of proteins essential for digestion and nutrient absorption. CF treatments include antibiotics to prevent lung infections, anti-inflammatory medicines to reduce inflammation, bronchodilators to improve airflow, and CFTR modulators to enhance faulty protein function (*Treatment | NHLBI, NIH*, 2023). Genetic testing helps determine if a treatment is effective because not everyone responds to it.

Mucus thinners are also used to clear mucus from the airways. CF patients with severe lung problems may need oxygen therapy, pulmonary rehabilitation, or ventilator support. Extracorporeal Membrane Oxygenation (ECMO) can help with oxygenation but has risks. Current treatments have limitations, as not all patients respond the same due to genetic differences, and treatments can be expensive, and require lifelong use. Antibiotics and other symptomatic treatments deal with respiratory problems but not their underlying causes (*About Cystic Fibrosis*, 2024). Since there is currently no cure, it is crucial to develop new treatments that target genetic causes for a large group of patients. Our aim is to create a small molecule treatment that targets the underlying causes of CF, according to FDA, EMA, and ACCESS regulatory standards to improve its effectiveness for patients worldwide.

## Rationale

Treating CF typically involves a combination of medications that attempt to target the underlying cause of the disease; however, due to genetic variations this path can be challenging and may not be effective for all patients. The primary breakthrough in CF treatment has been the

approval of CFTR modulators which targets and improves the function of the defective CFTR protein. Protein rectifiers are a step in the right direction, but the problem that persists is the complexity of treatment which also include symptomatic treatment and physiotherapy concomitantly. Most "corrector" drugs currently in development target older children, specifically those aged 6–12 years or above 12. Moreover, these drugs often pose significant risks, including severe liver-related and other side effects, and come with high costs (Rafeeq & Murad, 2017).

Our focus is in the development and marketing approval of a cutting-edge small molecule therapy, SION-109, to address the root causes of CF. This involves working with multiple regulatory agencies to ensure that SION-109 meets the necessary safety and efficacy standards. SION-109 is designed to target the most common genetic mutation affecting cystic fibrosis (CF) patients, ΔF508, with the goal of normalizing CFTR function. SION-109 is intended to enhance the stabilizing effect of SION-638 by targeting the interface between the NBD1 and intracellular loop 4 (ICL4) regions of the CFTR protein. Together, these therapies work to achieve complete restoration of CFTR function (Bryson, 2024). As previously stated, this treatment will be most effective in those with the most common mutation resulting in a substantial global positive outcome. In our efforts to enhance global access, we are prioritizing the development of critical regulatory frameworks, as effective CF treatment will transform the lives of individuals by offering them hope, improved quality of life, and increasing their life expectancy.

## Opportunity

A therapeutic approach directly targeting the CFTR gene mutations in CF holds substantial clinical promise by addressing the underlying defect rather than merely managing symptoms. CF, primarily caused by dysfunctional CFTR proteins due to genetic mutations, leads

to severe respiratory and digestive issues through thick mucus buildup, resulting in chronic lung infections, inflammation, and malnutrition (Cutting, 2015). Small molecule therapies, such as SION-109, that target CFTR mutations could significantly reduce these complications by restoring chloride transport and thinning mucus, potentially slowing lung function decline and decreasing infection rates (Rosen et al., 2018; Sionna Therapeutics, 2024).

Emerging CFTR modulators, including drugs like SION-109, which aim to correct or enhance CFTR protein function, have shown promising results in clinical studies. For instance, studies on CFTR potentiators and correctors have demonstrated improved lung function, quality of life, and reduced exacerbation frequency among patients with specific mutations (Rowe et al., 2017). This targeted approach could lead to personalized CF therapy, focusing on individual genetic profiles, a method that has already shown increased efficacy in some patient groups.

The clinical relevance of such advancements is amplified by regulatory support across agencies like the FDA, ACCESS, and EMA, which prioritize CF therapies due to the substantial unmet medical need. The FDA offers programs like Orphan Drug and Breakthrough Therapy designations to accelerate approval timelines for innovative treatments (Davies et al., 2020). EMA's pathways, including the Orphan Drug designation, provide incentives such as market exclusivity, scientific advice, and fee reductions, facilitating faster approval of CFTR modulators across the EU. Similarly, through collaborative review processes across Australia, Canada, Switzerland, Singapore, and the United Kingdom, ACCESS expedites the approval of treatments like SION-109 by allowing concurrent submissions and collaborative evaluations. This support underscores the feasibility of efficiently bringing CFTR-targeting small molecule therapies like SION-109 to market, making them a promising focus for future CF drug development (Davies et al., 2020).

## Development

SION-109 is an innovative CFTR modulator designed to correct the malfunction of the CFTR protein in patients with CF, specifically targeting the ΔF508 mutation. The primary objective of the clinical development program is to evaluate SION-109's safety, efficacy, and tolerability, ultimately comparing it to the current standard of care for CF patients. Given the limited number of existing CF treatments that target underlying CFTR defects, particularly Trikafta (elexacaftor/tezacaftor/ivacaftor) and other combination modulators, SION-109's development will focus on demonstrating added benefits over these standards in terms of CFTR function improvement, quality of life, and reduced morbidity (Keating et al., 2018).

### Phase I: Safety and Pharmacokinetics

The initial phase will focus on safety, tolerability, and pharmacokinetic (PK) profiling of SION-109 in healthy volunteers and potentially a small cohort of CF patients to assess preliminary pharmacodynamics (PD) in those with ΔF508 mutations.

**Objectives:**

1. Establish the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs).
2. Gather PK data to understand the drug's absorption, distribution, metabolism, and excretion.
3. Obtain preliminary PD data on CFTR correction and chloride transport.

**Study Design:**

- **Study Population:** A double-blind, placebo-controlled, dose-escalation study in healthy volunteers, followed by CF patients with the ΔF508 mutation in a secondary cohort.
- **Methodology:** Multiple ascending doses to identify the MTD, followed by single and multiple-dose cohorts in CF patients.
- **Endpoints:** Safety (adverse events, lab abnormalities), PK parameters, and exploratory PD markers -sweat chloride levels, nasal potential difference (Wainwright et al., 2015).

**Consideration of Standard of Care:** The focus at this stage is on safety rather than comparison to Trikafta or other standard-of-care treatments. However, exploratory biomarkers like sweat chloride provide early efficacy indicators that may predict SION-109's potential in Phase II trials (Keating et al., 2018).

## Phase II: Dose-Finding and Preliminary Efficacy

The Phase II trials will determine the optimal dose and regimen of SION-109 in a larger cohort of CF patients. Here, efficacy outcomes become a significant focus alongside continued safety monitoring.

**Objectives:**

1. Identify the optimal dose that balances efficacy with safety for Phase III trials.
2. Establish preliminary efficacy data through biomarkers and patient-reported outcomes.
3. Assess changes in lung function, quality of life, and infection rate reduction in CF patients.

**Study Design:**

- **Study Population:** CF patients with the ΔF508 mutation, randomized to receive SION-109 at varying doses or placebo.
- **Methodology:** Multi-center, randomized, double-blind, placebo-controlled study, possibly with crossover to allow within-subject comparisons.
- **Endpoints:**
    - Primary endpoints: Change in sweat chloride levels, as well as forced expiratory volume in 1 second (FEV1) as a measure of lung function (Zaher et al., 2021).
    - Secondary endpoints: Respiratory symptoms, CFQ-R (Cystic Fibrosis Questionnaire-Revised) scores for quality of life, and exacerbation frequency (Quittner et al., 2011).

**Comparison to Standard of Care:** Trikafta's efficacy in improving FEV1 and reducing exacerbations serves as a benchmark (Zaher et al., 2021). SION-109 must demonstrate an improvement either on par with or exceeding this standard, potentially targeting patients with residual unmet needs or those unresponsive to current modulators. Additional endpoints such as reduction in infection rates and improved gastrointestinal function may provide a competitive advantage if shown to be statistically significant.

## Phase III: Large-Scale Efficacy and Safety Trials

Phase III trials are critical to establish SION-109's efficacy and safety profile in a broad population, with the aim of regulatory approval. Given the high unmet need in CF, an ambitious approach in designing robust Phase III studies will focus on demonstrating SION-109's benefits over or in addition to the standard of care, especially targeting patient populations inadequately served by existing therapies.

**Objectives:**

1. Confirm efficacy across diverse CF patient demographics, including age groups and baseline lung function levels.
2. Validate long-term safety and tolerability of SION-109 in the CF population.
3. Position SION-109 as a first-line treatment option or as part of combination therapy for patients with the ΔF508 mutation.

**Study Design:**

- **Study Population:** A larger, global cohort of CF patients with ΔF508 mutation, potentially including those with heterozygous or homozygous variants.
- **Methodology:** Double-blind, randomized, placebo-controlled trials conducted over 48 to 52 weeks, with three treatment arms:
    - SION-109 monotherapy
    - SION-109 combined with current standard modulators (e.g., Trikafta)
    - Placebo or current standard modulator alone
- **Endpoints:**
    - **Primary Endpoint:** Change in FEV1 over baseline compared to placebo and/or standard care.
    - **Secondary Endpoints:** Frequency of pulmonary exacerbations, hospitalization rates, CFQ-R scores, nutritional status (BMI), and biomarkers like sweat chloride.
    - **Safety Endpoints:** Incidence of adverse events, particularly long-term effects such as liver function changes, as CFTR modulators are known to impact liver health.

**Comparison to Standard of Care:** The trial will emphasize the statistical superiority (or non-inferiority) of SION-109 alone or in combination with existing CF modulators. In particular, achieving a clinically meaningful improvement in FEV1 and reducing the rate of exacerbations will be essential. Additionally, SION-109's impact on patient-reported outcomes like quality of life and treatment adherence could enhance its profile compared to the standard of care.

**Additional Considerations:**

- **Patient Subpopulations:** Subgroup analyses for different CFTR mutation combinations and age demographics will determine if SION-109 can address needs beyond ΔF508 alone.
- **Long-Term Safety Study:** A subset of patients from Phase III may continue into an open-label extension to provide additional data on long-term safety and effectiveness, critical for the chronic nature of CF treatment.
- **Real-World Evidence (RWE):** Post-approval studies could be conducted to compare real-world efficacy, adherence, and patient satisfaction between SION-109 and existing therapies, leveraging RWE to support regulatory and reimbursement discussions.

## Development Rationale

The clinical development of SION-109 represents a targeted approach to CF treatment, aiming to surpass current standards by directly addressing CFTR dysfunction in ΔF508 mutation patients. Each phase of the development program builds towards establishing SION-109 as either a standalone or combination therapy, with Phase III trials designed to demonstrate clear clinical benefits over existing CFTR modulators. Given the significant regulatory support for CF

therapies, SION-109 has a feasible path to expedited review, provided it shows meaningful improvements in lung function, exacerbation rates, and quality of life for CF patients.

## Global Regulatory Strategy

### Post-Market Authorization submissions

Our initial focus will be on populations where cystic fibrosis (CF) is most prevalent. According to the Centers for Disease Control and Prevention (CDC), approximately 35,000 individuals in the U.S. are impacted by this genetic condition. In Australia, CF affects roughly 1 in every 2,500 to 1 in every 3,500 live births, a trend similar to other regions with significant populations of European descent (Guo et al., 2022). The highest global rates of cystic fibrosis are observed in countries such as the UK and Ireland, where it occurs in about 1 in every 2,500 live births (McBennett et al., 2021).

SION-109 will continue to undergo rigorous evaluation standards to ensure continued approval from the FDA, ACCESS, and EMA programs. The FDA and the EMA play crucial roles in the United States and Europe. The ACCESS initiative, which is led by Australia's TGA, is a collaborative effort that involves regulatory agencies from Australia, Canada, Switzerland, United Kingdom, and Singapore. The clinical development plan will comply with agency/consortium requirements to file for approval in their respective countries/markets.

The intent is to initiate marketing approval of SION-109 in the US and then take advantage of the ACCESS Initiative to obtain approval in the UK, Australia, Canada, Singapore, and Switzerland. Regulatory authorities in these countries collaborate to align regulations and

reduce duplicating review processes. Marketing authorization in the EU will also be pursued in parallel to submission to the ACCESS Initiative.

The IND application to the FDA will include the request for the Fast Track and Accelerated Approval Pathway. The FDA designed Fast Track as a means to expedite the review of drugs intended to treat serious conditions with no other current treatment options. This pathway provides the advantage of continuous discussion with the FDA regarding the development plan and the type of trials that would collect the appropriate data needed to support fast track designation and expedited approval. Open dialogue with the FDA lends to improving the efficiency of drug development and the review process.

Upon completion of Phase I-III trials and obtaining significant efficacy data to support accelerated approval, the New Drug Application (NDA) will be submitted. As a condition of accelerated approval, post-marketing monitoring and FDA reporting will be required to ensure risks are effectively managed and balanced as compared to benefits. Safety and efficacy analysis of SION-109 will remain top priority.

After accelerated FDA approval the subsequent strategy is to utilize the US Australia's partnership in the ACCESS Initiative to gain approval with the Therapeutic Goods Administration (TGA), followed by requesting review in the other regulatory agencies participating in this initiative. The ACCESS Initiative's sole goal is increasing international cooperation, reducing duplication, and ensuring timely access to high-quality medicines. A significant benefit of this program is the marketing application review is distributed in a manner that takes advantage of each agency's strengths and allows each agency to confidently accept the

assessments made by the other regulatory authorities. Responsibility is shared by the partners, reducing duplication of efforts and the time that patients gain access to new therapies.

Via the ACCESS Initiative, the TGA will also evaluate the clinical data to ensure safety, efficacy, and quality of SION-109 prior to issuing an approval to market the treatment in Australia. Again, the countries participating in this initiative will both respect the decisions of the other participating agencies, but will conduct their own safety assessments and may decline approval in their country or require additional information.

The accelerated pathway will also be pursued in the European Union (EU) in parallel to the ACCESS Initiative application. New cutting-edge medicines in the EU are evaluated by the European Medicines Agency (EMA) and authorized by the European Commission for marketing. As SION-109 is for the treatment of a rare condition, it will be submitted via the centralized procedure which requires only a single application to be submitted to obtain authorization across the European Union. The European Commission will provide authorization based on the scientific evaluation conducted by the EMA and their affirmative recommendation. Approval of the centralized marketing authorization will allow the marketing of SION-109 in all EU Member States as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway.

Ongoing post-authorization studies will be planned and conducted in the US, UK, Australia, Canada, Singapore, and Switzerland to facilitate monitoring of safety in the different demographic areas.

## Post-Authorization Activities

We will continue to closely monitor the performance of SION-109 among the general public in real-world settings. This evaluation phase is critical as it allows us to assess how the treatment affects individuals from various backgrounds and health profiles over extended periods. By observing the effects of SION-109 in these different populations, we can gather valuable insights regarding its efficacy and safety. Additionally, we will finalize the prescribing information, which will be comprehensive and include detailed guidelines and protocols for healthcare professionals. This document will outline the appropriate use of SION-109, including dosing instructions, potential side effects, and recommendations for monitoring patient outcomes. Our goal is to ensure that healthcare providers can administer SION-109 accurately and safely, maximizing its therapeutic benefits for patients while minimizing any associated risks.

After SION-109 is introduced, our primary focus will be to ensure the medication is accessible to people in need, safe for patients, and successful in addressing illnesses. We are dedicated to upholding international regulatory requirements to ensure that every stage of the drug's lifecycle is appropriately managed. The strategies we will use after SION-109 is released are Post Market Surveillance (PMS), long-term safety and efficacy studies, Risk Management Plan (RMP), education and awareness campaigns, and enhancing real-time feedback. PMS monitors the safety of SION-109 after its release. We will track adverse events (AEs) reported by healthcare providers and patients and submit regular safety reports to the FDA, EMA as required by regulators in the ACCESS consortium. The FDA keeps track of adverse events like side effects and overdose cases. They use this data to change drug labels and, in rare situations, reconsider their approval or marketing decisions (Research, 2020). We will also focus on

emerging safety concerns, particularly rare effects like liver toxicity, and use patient registries and electronic health records to collect real-world data.

Post Authorization Safety Studies (PASS), a type of long-term safety and efficacy research, can help evaluate an approved medication to identify safety issues, confirm its safety profile, or assess how well risk management strategies are working (*Post-authorisation Safety Studies (PASS) | European Medicines Agency (EMA)*, 2012). PASS will determine the long-term safety profile of SION-109, focusing on lever functions, secondary infection risks, and other specific toxicities. We will create a custom RMP to comply with local regulations, including the FDA's REMS in the U.S. and EMA requirements in the EU. We will actively manage hazards like drug interactions and liver damage by training medical professionals to monitor patients' health effectively. We will conduct training workshops for medical professionals on the safe use and prescription of SION-109 for various age groups and CFTR mutations to inform and raise awareness about the medication. Additionally, we will develop and provide resources, such as a mobile app that can help patients access more information on the benefits and risks of the medicines, track dosing reminders, and gather feedback from patients and providers, which can help us track the effectiveness and safety of the medication.

We will actively leverage Real-World Evidence (RWE) to ensure SION-109 remains safe, effective, and accessible. Collecting and analyzing Real-World Data (RWD) from diverse sources, including patient registries, electronic health records (EHRs), mobile health applications, and adverse event reporting systems, we aim to comprehensively understand the medication's real-world impact. This approach will complement our PMS and PASS post-marketing activities while providing additional insights into treatment outcomes across various patient populations (Sherman et al., 2016). By systematically integrating RWE into our

post-marketing activities, we aim to enhance regulatory compliance, improve patient outcomes, and contribute to the broader understanding of CF treatment in real-world settings.

## References

*About cystic fibrosis*. (2024, May 15). Cystic Fibrosis. https://www.cdc.gov/cystic-fibrosis/about/index.html

*Authorisation of medicines | European Medicines Agency (EMA)*. (2019, April 3). European Medicines Agency (EMA). https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

Bryson, S. (2024, January 25). Phase 1 trial of SION-109 oral therapy doses first volunteer. *Cystic Fibrosis News Today*. https://cysticfibrosisnewstoday.com/news/phase-1-trial-sion-109

Cutting, G. R. (2014). Cystic fibrosis genetics: from molecular understanding to clinical application. *Nature Reviews Genetics*, *16*(1), 45–56. https://doi.org/10.1038/nrg3849

Davies, J. C., Alton, E. W. F. W., & Bush, A. (2007). Cystic fibrosis. *BMJ*, *335*(7632), 1255–1259. https://doi.org/10.1136/bmj.39391.713229.ad

*Global and regional regulatory harmonization initiatives*. (2011, May 23). https://www.who.int/teams/regulation-prequalification/regulation-and-safety/regulatory-convergence-networks/harmonization

Guo, J., Garratt, A., & Hill, A. (2022). Worldwide rates of diagnosis and effective treatment for cystic fibrosis. *Journal of Cystic Fibrosis*, *21*(3), 456–462. https://doi.org/10.1016/j.jcf.2022.01.009

*International Recognition Procedure*. (2024, August 29). GOV.UK. https://www.gov.uk/government/publications/international-recognition-procedure/international-recognition-procedure

Kreindler, J. L. (2009). Cystic fibrosis: Exploiting its genetic basis in the hunt for new therapies. *Pharmacology & Therapeutics*, *125*(2), 219–229. https://doi.org/10.1016/j.pharmthera.2009.10.006

McBennett, K. A., Davis, P. B., & Konstan, M. W. (2021). Increasing life expectancy in cystic fibrosis: Advances and challenges. *Pediatric Pulmonology*, *57*(S1). https://doi.org/10.1002/ppul.25733

*Obtaining an EU marketing authorisation, step-by-step | European Medicines Agency (EMA)*. (2021, May 3). European Medicines Agency (EMA). https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/obtaining-eu-marketing-authorisation-step-step?form=MG0AV3

Office of the Commissioner. (2018, January 4). *Step 3: Clinical research*. U.S. Food And Drug Administration. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research

Office of the Commissioner. (2024, August 13). *Fast track*. U.S. Food And Drug Administration. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track

*Post-authorisation safety studies (PASS) | European Medicines Agency (EMA)*. (2012, February 10). European Medicines Agency (EMA). https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/post-authorisation-safety-studies-pass

Quittner, A. L., Sawicki, G. S., McMullen, A., Rasouliyan, L., Pasta, D. J., Yegin, A., & Konstan, M. W. (2011). Psychometric evaluation of the Cystic Fibrosis

Questionnaire-Revised in a national sample. *Quality of Life Research*, *21*(7), 1267–1278. https://doi.org/10.1007/s11136-011-0036-z

Rafeeq, M. M., & Murad, H. a. S. (2017). Cystic fibrosis: current therapeutic targets and future approaches. *Journal of Translational Medicine*, *15*(1). https://doi.org/10.1186/s12967-017-1193-9

Research, C. F. D. E. A. (2020, April 2). *Postmarketing surveillance programs*. U.S. Food And Drug Administration. https://www.fda.gov/drugs/surveillance/postmarketing-surveillance-programs

Rowe, S. M., Daines, C., Ringshausen, F. C., Kerem, E., Wilson, J., Tullis, E., Nair, N., Simard, C., Han, L., Ingenito, E. P., McKee, C., Lekstrom-Himes, J., & Davies, J. C. (2017). Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *New England Journal of Medicine*, *377*(21), 2024–2035. https://doi.org/10.1056/nejmoa1709847

Sherman, R. E., Anderson, S. A., Pan, G. J. D., Gray, G. W., Gross, T., Hunter, N. L., LaVange, L., Marinac-Dabic, D., Marks, P. W., Robb, M. A., Shuren, J., Temple, R., Woodcock, J., Yue, L. Q., & Califf, R. M. (2016). Real-World evidence — What is it and what can it tell us? *New England Journal of Medicine*, *375*(23), 2293–2297. https://doi.org/10.1056/nejmsb1609216

Sionna Therapeutics. (2024, January 24). *Sionna Therapeutics announces Phase 1 initiation for SION-109 in Cystic Fibrosis - Sionna Therapeutics*. https://www.sionnatx.com/press-releases/sionna-therapeutics-announces-phase-1-initiation-for-sion-109-in-cystic-fibrosis/

*Treatment | NHLBI, NIH*. (2024, November 15). NHLBI, NIH. https://www.nhlbi.nih.gov/health/cystic-fibrosis/treatment

Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., Colombo, C., Davies, J. C., De Boeck, K., Flume, P. A., Konstan, M. W., McColley, S. A., McCoy, K., McKone, E. F., Munck, A., Ratjen, F., Rowe, S. M., Waltz, D., & Boyle, M. P. (2015). Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508delCFTR. *New England Journal of Medicine*, *373*(3), 220–231. https://doi.org/10.1056/nejmoa1409547

*What is cystic fibrosis? | NHLBI, NIH*. (2024a, November 15). NHLBI, NIH. https://www.nhlbi.nih.gov/health/cystic-fibrosis

Zaher, A., ElSaygh, J., Elsori, D., ElSaygh, H., & Sanni, A. (2021). A review of TriKafTa: Triple Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulator therapy. *Cureus*. https://doi.org/10.7759/cureus.16144