A Randomized, Two-Period, Two-Arm, Double-Dummy, Crossover Study to Compare Natriuretic Effects of Extended Release Torsemide to Immediate Release Torsemide in Patients With Heart Failure (NEXT-HF)

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1. Study Title

A Randomized, Two-Period, Two-Arm, Double-Dummy, Crossover Study to Compare Natriuretic Effects of Extended Release Torsemide to Immediate Release Torsemide in Patients with Heart Failure (NEXT-HF).

2. Investigators

Principal Investigator: [redacted]

Co-Investigator: [redacted]

3. Summary

Excessive sodium and water retention is a hallmark of heart failure, contributing significantly to morbidity and mortality. Effective renal clearance of sodium and water remains one of the most challenging aspects of heart failure management, particularly given the difficulty patients face in adhering to a low-sodium diet. Conventional loop diuretics have a short duration of action, often leading to a renal adaptive effect—where the diuretic action of a morning dose diminishes by midday, allowing sodium and water retention to accumulate after each meal. This cycle of intermittent fluid loss, followed by fluid retention can eventually result in diuretic resistance and an inadequate fluid loss, leading to decompensation, hospitalization, and repeated exacerbations of heart failure.

Sarfez Inc. has developed an extended-release formulation of torsemide designed to provide prolonged diuretic action, maintaining sodium excretion for several hours post-dosing. The primary objective of this study is to evaluate whether a morning dose of extended-release torsemide enhances renal sodium excretion after lunch (4-8 hours after dosing) compared to immediate-release torsemide.

This is a randomized, double-blind, crossover study in patients with heart failure who are on a stable dose of a loop diuretic. During the study period, participants' current loop diuretics will be replaced with an equivalent dose of either immediate-release or extended-release torsemide.

Following a one-week stabilization period on the assigned torsemide formulation, patients will report to the clinical site for an assessment visit. On the study day, patients will take a single dose of the same torsemide formulation they have been on for the past week, administered after breakfast. Urine samples be collected are:

- 0–4 hours post-dosing (pre-lunch period)
- 4–8 hours post-dosing (post-lunch period)
- 8–24 hours post-dosing (24 hours period)

The primary endpoint will be urinary sodium excretion (4-8 hours after dosing). This will be compared between the extended-release arm and the immediate-release arm to assess the efficacy of prolonged diuretic action. In addition, urinary potassium and creatinine excretion and creatinine clearance will be measured in all urine samples as the safety endpoints.

4. Background

Heart failure (HF) is characterized by fluid overload and pulmonary congestion, primarily driven by inappropriate renal sodium and water retention or redistribution of blood volume from the splanchnic to the central circulation. As a result, a key aspect of HF management is preventing or reversing the accumulation of sodium and fluid. This requires the use of potent diuretics alongside dietary sodium and fluid restriction.

In clinical practice, most patients with more than mild HF receive a loop diuretic and are advised to limit sodium intake to 2-3 grams (80-120 mmol) per day. While these strategies are widely accepted, they often prove inadequate. Many patients experience recurrent fluid retention and congestion, leading to frequent hospitalizations, reduced quality of life, and poor long-term outcomes. The reasons for these treatment failures are multifaceted and may include:

- Development of diuretic resistance or tolerance
- Non-adherence to diuretic therapy
- Excessive dietary sodium intake
- Short duration of action of conventional loop diuretics

Loop diuretics such as furosemide, bumetanide, and torsemide have a mean duration of action of approximately 3–4 hours in healthy individuals, with a slightly prolonged effect in patients with heart failure (HF) or chronic kidney disease (CKD). However, once the drug is cleared from circulation, the kidneys may reabsorb much of the sodium and water in the diet, potentially reversing the diuretic-induced fluid loss. This post-diuretic sodium retention can lead to cyclical fluctuations in sodium resulting in inappropriate activation and suppression of the renin-angiotensin-aldosterone system (RAAS). The effect is further exacerbated when patients consume a high-sodium meal more than four hours after their morning diuretic dose, as the drug is no longer present to counteract sodium reabsorption.

Sarfez Inc. has developed an extended-release (ER) formulation of torsemide, designed to provide prolonged diuretic action and mitigate the limitations of immediate-release (IR) loop diuretics. Among loop diuretics, torsemide exhibits less variability in pharmacokinetics and is primarily metabolized by the liver, rather than the kidneys—making its bioavailability more stable in patients with HF and CKD. Additionally, torsemide has been shown to exert partial mineralocorticoid receptor antagonist (MRA) and anti-fibrotic effects, which may enhance its efficacy in HF management while reducing potassium loss. The novel extended-release torsemide formulation is now FDA-approved and marketed as SOAANZ®.

A prior clinical trial comparing 20 mg of SOAANZ® to 20 mg of generic torsemide in healthy volunteers consuming a high-sodium diet (300 mmol/day) demonstrated that SOAANZ® provided enhanced and sustained natriuresis. The study found that:

- Early sodium excretion (0–2 hours post-dose) was lower with SOAANZ® than with immediate-release torsemide.
- Late sodium excretion (8–13 hours post-dose) was significantly greater, suggesting prolonged diuretic action.
- Overall, 24-hour sodium excretion was significantly greater with SOAANZ.
- The glomerular filtration rate (GFR) assessed from creatinine clearance, was reduced over 24 hours after torsemide IR, but not reduced significantly after SOAANZ.

These findings suggest that extended-release torsemide may facilitate the elimination of sodium from meals consumed 4 hours after dosing, potentially reducing sodium retention and congestion in HF patients.

This study aims to test the hypothesis that patients with HF retain less sodium from a meal consumed approximately 4 hours after a dose of extended-release torsemide compared to an equivalent dose of immediate-release torsemide.

A recent pharmacokinetic study of a new ER torsemide formulation found that 24 mg of ER torsemide provides equivalent bioavailability (AUC) to 20 mg of generic IR torsemide. Based on this, Sarfez Inc. has filed an Investigational New Drug (IND) application (IND# 122065) with the FDA to evaluate this dosage form. Accordingly, in this study, 24 mg of extended-release torsemide will be compared with 20 mg of immediate-release torsemide.

5. Specific Aims

5.1. Primary Endpoint

The primary endpoint of the study is urinary sodium excretion measured after dosing:

- 4–8 hours (post-lunch period)

5.2. Secondary Endpoints

The secondary endpoints are urinary sodium excretion after dosing:

1. 0–4 hours (pre-lunch period)
2. 8–24 hours (post-lunch period)
3. Safety endpoints include:
    - Creatinine clearance (0-4, 4-8, and 8-24 hours after dosing)
    - Urinary potassium excretion (0-4, 4-8, and 8-24 hours after dosing)

6. Research Plan

6.1. Study Design

This is a double-blind, double-dummy, two-period, two-arm, randomized, crossover study.

6.2. Study Population

The study population will consist of 20 men and women, aged 18 years and older, with a known history of heart failure (HF) as diagnosed by a cardiologist. These participants must have been in a stable (compensated) phase of HF for at least one month prior to randomization and have been prescribed oral furosemide (20 mg to 80 mg daily) or equivalent doses of torsemide or bumetanide for approximately 30 days prior to the study.

6.3. Inclusion Criteria

Participants must meet the following criteria:

1. **Age**: 18 years or older.
2. **Informed Consent**: Willing and able to sign the informed consent form.

3. **Stable Chronic HF**À A clinical diagnosis of chronic heart failure considered stable by the patient's cardiologist/physician or another experienced clinician for at least one month prior to randomization.
4. **Current Diuretic Therapy**ÀReceiving an oral dose of 20 mg to 80 mg daily of furosemide, or 10 mg to 40 mg daily dose of torsemide, or 1 mg to 4 mg daily dose of bumetanide, for about 30 days prior to randomization.
5. **Stable HF Medications**: No anticipated changes in HF medications during the study period.
6. **Female Participants**À Premenopausal women of childbearing potential must have a negative pregnancy test prior to study initiation and agree to use effective contraceptive methods throughout the study period.

6.4. Exclusion Criteria

Participants will be excluded from the study if they meet any of the following conditions:

1. **Other Diuretics**: Requirement for a diuretic other than furosemide, bumetanide, or torsemide (except for spironolactone, eplerenone, finerenone, or SGLT2 inhibitors) at randomization or during the study.
2. **Recent Cardiovascular Events**: Myocardial infarction, stroke, transient ischemic attack, acute kidney injury, or acute HF requiring hospitalization within 30 days prior to randomization.
3. **Severe Lung Disease**: Severe or symptomatic lung disease or respiratory symptoms distinct from HF.
4. **Urinary Issues**: History of urinary incontinence, or inability to empty the bladder.
5. **Uncontrolled Comorbidities**: Uncontrolled diabetes mellitus or hypertension.
6. **Renal Dysfunction**: Estimated GFR < 30 ml/min/1.72m².
7. **Cardiac Conditions**: History of flash pulmonary edema or amyloid cardiomyopathy.
8. **Breastfeeding**: Female participants who are breastfeeding.
9. **Recent Participation in Clinical Trials**À Participation in another clinical trial within the last three months prior to randomization.
10. **Requirements for treatment** with a non-steroidal anti-inflammatory drug (except for Aspirin up to 200 mg as PRN daily).
11. **Serum potassium concentration** <3.5 or >5.5 mmol/L.

6.5. Study Flow

6.5.1. Initial Study Procedures

- **Identification of Participants**ÀPatients with a known history of stable heart failure (HF) for at least one month will be identified through healthcare records at clinical site, heart failure clinic, nephrology clinic, and other relevant clinics. Additionally, providers likely caring for these patients will be contacted to identify potential participants.

- **Informed Consent**: The purpose and procedures of the study will be explained to the potential participants, and they will have the opportunity to ask questions (as per Good Clinical Practice Guidelines). A copy of the informed consent form will be provided for review. After reading the consent, participants will be given a chance to ask questions again before deciding whether to sign the consent form. The study will follow regulatory protocols, ensuring that protected health information is accessed only by qualified study team members and for necessary purposes.
- **Physical Examination**: A physical examination will be conducted at the screening visit and at visit 4 (final study visit), including edema status.
- **Vital Signs:** Vital signs will be recorded at every visit (e.g., temperature, blood pressure, heart rate, breathing rate).
- **Eligibility Check**: After informed consent, participants will be assessed for inclusion and exclusion criteria. Blood samples will be collected for a complete metabolic panel (CMP-14) with eGFR.
- **Randomization**: Participants who meet all inclusion and exclusion criteria will be randomly assigned to one of two arms (Arm 1 or Arm 2), according to a pre-defined randomization schedule managed by the site pharmacy. This approach ensures blinding for both the participants and the investigators.

6.5.2. Treatment Arms and Crossover Design

- **Arm 1**: Approximately half of the participants will receive 20 mg IR torsemide followed by 24 mg ER torsemide or 40mg IR torsemide followed by 48 mg ER torsemide (6-10 days each).
- **Arm 2**: The other half will receive 24 mg ER torsemide followed by 20 mg IR torsemide, or 48 mg ER torsemide followed by 40 mg IR torsemide (6-10 days each).
- **Dose Conversion**:
    - Patients on 20-40 mg furosemide will be converted to 20 mg IR torsemide or 24 mg ER torsemide.
    - Patients on 60-80 mg furosemide will be converted to 40 mg torsemide (two 20 mg tablets) or 48 mg ER torsemide (two 24 mg tablets).
    - Patients on 1 mg bumetanide will be converted to 20 mg IR torsemide or 24 mg ER torsemide, while those on 2 mg bumetanide will be converted to 40 mg torsemide or 48 mg ER torsemide.
- **Double-Dummy Design**: To maintain blinding, participants will also receive placebo corresponding to the medications in their arm, ensuring that participants and investigators remain unaware of their treatment assignment.
- **Dietary Instructions**: Participants will be instructed to follow a low-sodium diet with a daily intake of approximately 3 grams of sodium throughout the study period.

6.5.3. Test Day Procedures

The test day will occur on the last day of each treatment period, with participants staying at the site for 9-10 hours (no overnight stay). The study staff undertake the following:

- **Medication Compliance**: Collect study medications for pill count and assess compliance.

- **Dosing**
  - A standard breakfast will be served 30 minutes before dosing, and participants will be instructed to complete it within 30 minutes.
  - After completion of breakfast, participants will receive study medication along with 350 ml +/- 20 ml water.
- **Post-dose Sample Collection**
  - Urine samples will be collected at 0-4 hours and 4-8 hours after dosing. For each time point, total volume will be measured, and two 5 ml aliquots will be taken for sodium, potassium, and creatinine measurements. The remaining urine will be stored in a cool place for 48 hours or until laboratory results are sent to the site and reviewed by the PI for any discrepancy.
  - After 4 hours post-breakfast, a lunch containing salt will be served, and participants will complete it within 30 minutes.
  - Participants will not be permitted to eat except of the site provide breakfast and lunch, and they will be asked consume all the food (breakfast and lunch; no additional snacks or other food items).
  - Participants will be allowed to consume water, but no flavored drinks or sodas, as they require.
  - Participants will be reminded to empty their bladder completely during the each time point. Bladder emptying time (i.e., passing urine) and urine volume will be recorded.
  - After completion of the 4-8 hours urine collection, participants will be given a urine collection container and will be instructed to collect all the urine passed into the container until 24 hours after the dosing time (site will provide dosing time to the participants).
  - The container will be collected next morning by the site personnel, who will bring the container to site. Upon receiving the container, site staff will measure the volume, take two 5 ml aliquots for sample analysis.

6.5.4. Sample Collection Timepoints

- **Urine Samples**

  Post-dose
  - *Visit 3 (Test Day of Period 1):* Collect urine samples at 0-4 hours, 4-8 hours
  - *Continues collection at home:* 8-24 hours (measure and record total volume for each).
  - *Visit 4 (test day of Period 2):* Collect urine samples at 0-4 hours, 4-8 hours.
  - *Continues collection at home:* 8-24 hours (measure and record total volume for each).

- **Blood Samples:**
    - *Visit 1 (screening):* Collect 10-12 ml venous blood for whenever is convenient for CMP-14 with eGFR testing.
    - *Visit 3 (Test Day of Period 1):* Collect 10-12 ml venous blood in the morning before breakfast for CMP-14 with eGFR.
    - *Visit 4 (test day of Period 2):* Collect 10-12 ml venous blood in the morning before breakfast for CMP-14 with eGFR.

6.5.5. Analytes/Measurements

- **Blood Samples:**
    - *Screening:* CMP-14 with eGFR
    - *Test day of period 1:* CMP-14 with eGFR
    - *Test day of period 2:* CMP-14 with eGFR
- **Urine Samples:**
    - *Test Day (Post-dose 0-4, 4-8, and 8-24 hours):* Urine volume, sodium, potassium, and creatinine.

6.5.6. End of Study Procedures

At the end of the study period, participants will:

- Resume their pre-enrollment diuretic regimen.
- Continue routine follow-up with their physicians for standard care.

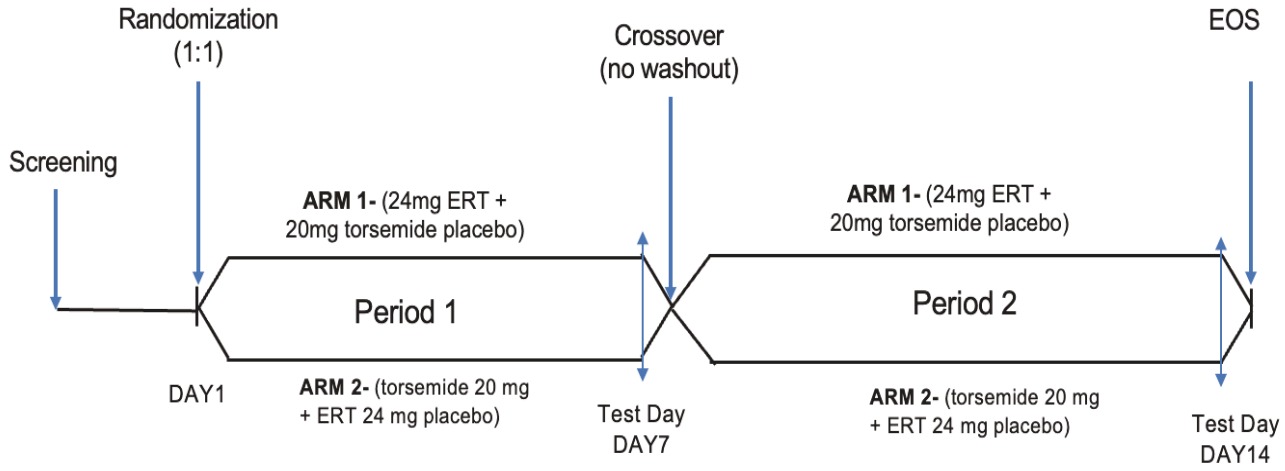


Figure 1. Study Flow Diagram

Dosing: Each patient will be given either two or four bottles (one or two active bottles, and one or two placebo bottles). The bottle-pair will be switched upon crossover.

Dose Conversion:

- Patients on a daily dose of 40 mg furosemide will receive either:
  - One bottle of 20 mg IR torsemide and one bottle of placebo (24 mg ER torsemide), or
  - One bottle of 24 mg ER torsemide and one bottle of placebo (20 mg IR torsemide).
- Patients on a daily dose of 80 mg furosemide will receive either:
  - Two bottles of 20 mg IR torsemide and two bottles of placebo (24 mg ER torsemide), or
  - Two bottles of 24 mg ER torsemide and two bottles of placebo (20 mg IR torsemide).
- Patients on 1 mg bumetanide will be converted to 20 mg IR torsemide or 24 mg ER torsemide, while those on 2 mg bumetanide will be converted to 40 mg torsemide or 48 mg ER torsemide.

6.6. Statistical Analysis

6.6.1. Primary Endpoint (4–8h Sodium Excretion)

Analysis

- **Metric:** Adjusted sodium excretion (Na/Cr ratio) over 4–8h for ER vs. IR.
  - **Rationale:** Urine collection timing may vary due to practical challenges in a crossover design. Normalizing sodium excretion to creatinine accounts for variability in urine flow rate and incomplete bladder emptying, ensuring robust comparison between ER and IR torsemide.
- **Method**
  - Compute within-subject differences in adjusted sodium excretion (ER – IR).
  - Test with Wilcoxon signed-rank test (non-parametric).
- **Effect Size**
- **Median difference** (ER-IR; Hodges-Lehmann estimator) with 95% confidence interval (CI) and p value <0.05.

Sensitivity Analysis

- **Metric:** Absolute sodium excretion (mmol) over 4–8h.
- **Method:** Wilcoxon signed-rank test (paired, non-parametric).
- **Effect Size:** Median difference (ER − IR) with 95% CI.

Justification for No Adjustment of p-Value

- **Single Primary Hypothesis:** Both metrics address the same hypothesis (*"Does ER increase sodium excretion vs. IR in 4–8h?"*), just with different measurement approaches (i.e., adjusted sodium excretion or absolute sodium excretion).
- **Hierarchical Testing:** To avoid type I error, we are pre-specifying adjusted Na/Cr as primary and absolute Na as sensitivity.

6.6.2. Secondary Endpoints (0–4h, 8–24h Sodium Excretion)

Analysis

- **Metric**: Total sodium excretion (mmol) for each interval.
- **Method**
  - Compute difference in sodium excretion (ER − IR) for each interval.
  - Apply Wilcoxon signed-rank test for both intervals.

- **Interpretation**
    - Report median differences and CIs, but interpret p-values as exploratory (no multiplicity adjustment needed because primary endpoint is strictly focused on 4–8h). 95% CI and p values < 0.05 (exploratory analyses and independent time intervals).

6.6.3. Safety Endpoints (Creatinine Clearance, creatinine and potassium excretion)

Analysis

- **Metric**: Difference in excretion of potassium and creatinine, and of creatinine clearance (ER-IR)
- **Method**
    - **Descriptive statistics**: Mean change (SD) (median IQR) for each treatment and each interval.
    - **Comparison**: Use paired Wilcoxon tests only if hypothesis-driven (e.g., pre-specified safety concerns about potassium).

6.6.4. Small Sample Size Considerations (n=20)

- **Power**: Limited power to detect small effects.
- **Focus on Precision**: Prioritize effect sizes with CIs over p-values (e.g., "The 95% CI excludes differences smaller than 8 mmol, suggesting a clinically meaningful effect").
- **Non-Parametric Tests**: Wilcoxon is preferred due to robustness to non-normality in small samples.

7. Subject Privacy and Protected Health Information

Subjects' protected health information will only be accessed by qualified study team members, and only when necessary, to fulfill the requirements of the approved study protocol. All information will be handled in compliance with regulatory protocols. The patient data will be stored securely, adhering to site-specific protocols, and will include both paper-based documents (e.g., informed consent forms and any source documents) and electronic records.

8. Possible Discomforts and Risks

Potential discomforts and risks associated with participation in this study include those related to phlebotomy, such as pain, bruising, bleeding, and, in rare cases, infection. The study involves loop diuretics at doses equivalent to those prescribed as standard care for each patient prior to enrollment. The risks associated with phlebotomy are minimal. Furthermore, all procedures will be conducted in a clinical research setting, with continuous observation and medical assistance readily available, including access to an emergency department and skilled staff.

9. Possible Benefits

While participation in this study is unlikely to offer direct benefits to the participants, the results could indirectly benefit patients with heart failure. Specifically, the findings may provide valuable insights into the effectiveness of this new formulation in managing sodium and water retention in this patient population.

10. Conflict of Interest

No conflicts of interest have been identified for this study.

11. Reporting Requirements for Serious Adverse Events (SAEs)

Reporting of SAEs from Investigator to Sponsor/Sponsor Designee:

If an investigator determines that an event qualifies as a Serious Adverse Event (SAE), it must be reported to the Sponsor or Sponsor designee within 24 hours of being informed. Any follow-up information on a previously reported SAE must also be communicated to the Sponsor within 24 hours.

If the investigator does not have all the details regarding an SAE, the event should still be reported within the required timeframe using the appropriate data collection tool. The investigator will provide an initial causality assessment at the time of the report, as outlined in Section 13, "Assessment of Causality."

Pregnancies:

For patient safety, any pregnancy that occurs during the study period (up to the final study visit) must be reported to the Sponsor within 24 hours. The pregnancy should be followed to determine the outcome, including spontaneous or voluntary termination, birth details, and any birth defects, congenital abnormalities, or complications for the mother or newborn. The postpartum follow-up period is 28 days. Pregnancy details should be reported by email to the Sponsor’s pharmacovigilance contact. Any SAE experienced during pregnancy must be documented on the SAE Report Form.

12. Meals Consideration

To maintain consistent sodium intake across visits, the site must procure the same meal from the same vendor for each patient at each visit.

Sponsor's Representative for Information:

Chris Wilcox, MD, PhD
8000 Towers Crescent Drive
Vienna, VA 22182
Telephone: +1-703-627-1934
Fax: +1-703-759-2565

13. Study Assessment Schedule

Study Assessment Schedule					
Procedure Description	Frequency of Procedures	Screening	Start of Period 1 (Randomization)	End of Period 1, Crossover, and Start of Period 2	End of Period 2, and End of Study
		V1	V2	V3 (test day)	V4 (test day)
Informed Consent	1	x			
Eligibility Check	1	x			
Demographic Characteristics	1	x			
Medical History	1	x			
Concomitant Medications	4	x	x	x	x
Vital Signs	4	x	x	x	x
Physical Examination	2	x			x
Randomization	1		x		
Crossover	1			x	
Drug Dispensing	2		x	x	
Drug accountability (counting)	2			x	x
Blood Samples for CMP-14 with eGFR[#]	3	x		x	x
Adverse Events (per patient /Period	2			x	x
Meal (constant for each subject in each period)	2			x	x
Urine Collection (on-site)*[$]	4			xx	xx
Urine Collection (at home)*	2			x	x
Pregnancy Test (child bearing age females)	1	x			

Note: [*]Urine will be collected 0-4 and 4-8 hours after dosing at the site, and 8-24 at home (site personnel will make sure to pick the 8-24 urine container and deliver it to the site next morning after each dosing day).

[$]On each test days, two urine samples (0-4 and 4-8 hours) will be collected.

No urine collection at screening. No pre-dose urine sample collection. All urine samples will be used to measure sodium, potassium, and creatinine.

[#]Blood samples will be collected in the morning before breakfast at visits 3 and 4. At the screening visit, blood sample will be collected as per the convenience of the site.

13. Assessment of Causality (Relationship to Study Drug)

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure. Qualifies as an Adverse Drug Reaction (ADR).
Probable	A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that could not be reasonably explained by the known characteristics of the study participant's clinical state.Qualifies as a Suspected Adverse Reaction (SAR).
Possible	A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; but that could readily be produced by a number of other factors. Qualifies as a Suspected Adverse Reaction (SAR).
Remote/Unlikely	A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or suspected response pattern to the suspected drug; but that could reasonably be explained by known characteristics of the study participant's clinical state.
Not Related	Adverse event is clearly due to extraneous causes(e.g.,underlyingdisease,environment).