PROTOCOL TITLE PAGE

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Efficacy of the Flush Advanced+ Dietary Supplement Drink Mix to Improve Urinary Health Measures

PROTOCOL NUMBER: BH-FADV-001

SPONSOR NAME Bonafide Health, LLC

LEGAL REGISTERED ADDRESS: 500 Mamaroneck Avenue, Suite 510, Harrison, NY, 10528

VERSION NUMBER: 2

VERSION DATE: 5/7/226

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Sponsor Signature/Agreement:

I have read and understand the attached protocol entitled **"A Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Efficacy of the Flush Advanced+ Dietary Supplement Drink Mix to Improve Urinary Health Measures"** and agree to the study design as described in the protocol procedures.

I agree that I have reviewed the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines per Good Clinical Practice (GCP) and am aware of my obligations and responsibilities as a sponsor.

_____ _____

Trisha VanDusseldorp **Date**

Senior Director, Clinical Research

Bonafide Health, LLC

_____ _____

James Komorowski **Date**

Chief Science Officer

Bonafide Health, LLC

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1. PROTOCOL SUMMARY

1.1. Synopsis

<table>
<tr><td>Name of Sponsor:</td><td>Bonafide Health, LLC</td></tr>
<tr><td>Study Product Name:</td><td>Flush Advanced+ (Uqora)</td></tr>
<tr><td>Protocol Title:</td><td>A Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Efficacy of the Flush Advanced+ Dietary Supplement Drink Mix to Improve Urinary Health Measures</td></tr>
<tr><td>Protocol Number:</td><td>BH-FADV-001</td></tr>
<tr><td>Study Design:</td><td>A randomized, placebo-controlled, parallel-allocation intervention trial</td></tr>
<tr><td>Study Objectives and Endpoints:</td><td>
<table>
<tr><th colspan="2">Purpose & Previous Approvals of Product Research</th></tr>
<tr><td colspan="2">The purpose of this research study is to evaluate the efficacy and safety of Flush Advanced+ in women with recurrent, bothersome urinary tract symptom episodes who are otherwise healthy.</td></tr>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>To determine the effect of Flush Advanced+ on recurrent, bothersome urinary tract symptom episodes over the course of 6 months of use</td><td>• Difference between treatment arms in total number of bothersome urinary tract symptom episodes over the course of the 6-month trial*</td></tr>
<tr><td></td><td>• Difference between treatment arms in total number of sex-triggered bothersome urinary tract symptom episodes over the course of the 6-month trial**
• Difference between treatment arms in total number of courses of antibiotics used for bothersome urinary tract symptom episodes over the course of the 6-month trial **</td></tr>
</table>
</td></tr>
</table>

	To determine the effect of Flush Advanced+ on impression of overall improvement	Difference between treatment arms and changes in individual scores across time in the change in improvement as measured by the PGIC at Baseline, Month 2, Month 4, and Month 6*
	To determine the effect of Flush Advanced+ on urinary health outcomes after 6 months of use	Difference between treatment arms and changes in individual scores across time in the following: • Symptom severity during recurrent, bothersome urinary tract symptom episodes as measured by UTI-SIQ-8, RUTISS Section C (RUTISS-C), and PGIS** • Ratio of self-reported good vs. bad urinary health days assessed via daily diaries**
	To determine the effect of Flush Advanced+ on sex-related quality of life (QOL)	Difference between treatment arms and changes in individual scores across time in the following: • Perception of urinary health symptoms' impact on sex life as measured by section 2 of RUTIIQ**
	To determine the effect of Flush Advanced+ on urinary health-related quality of life (QOL)	• Difference between treatment arms and changes in individual scores across time in Modified Recurrent Urinary Tract Infections Impact Questionnaire (m-RUTIIQ) from Baseline to EOS**
	To understand satisfaction with the Flush Advanced+ product	• Difference between treatment arms in Product Experience Questionnaire (PEQ) scores at months 1-6**

<table>
<tr><td></td><td>
*Denotes primary endpoints of study outcome measures.
**Denotes secondary endpoints of study outcome measures.
<table>
<tr><td colspan="2">Safety</td></tr>
<tr><td>To assess the safety and tolerability of Flush Advanced+ in women with recurrent, bothersome urinary tract symptom episodes</td><td>Reports of adverse events (AEs)</td></tr>
</table>
</td></tr>
<tr><td>Sample Size and Study Population:</td><td>This study will include 150 individuals who are biological females between the ages of 18-75 who have a history of recurrent, bothersome urinary tract symptom episodes. Please refer to Sections 5.1 and 5.3 for details on inclusion and exclusion criteria.</td></tr>
<tr><td>Study Duration and Interventions:</td><td>The randomized, placebo-controlled trial will be conducted for 6 months. There will be multiple methods used for recruitment: from HCP referrals, through external recruitment platforms, through Bonafide Health’s internal participant recruitment database, on social media platforms affiliated with Uqora and Bonafide Health, and with flyers.

HCPs may recruit patients with a history of bothersome urinary tract symptom episodes who they see in-clinic or via telehealth.

Alternatively, women who have signed up to be contacted for research by Bonafide Health may be alerted of the study by Bonafide Health research members via email or text.

The trial will also be advertised on external recruitment platforms. Users and subscribers of these platforms may express interest in the trial.

Lastly, the trial will be advertised on social media pages affiliated with Uqora and Bonafide Health advertisement in Section 10.3.1.

Hard copies of the advertisement in Section 10.3.1 may also be used to recruit participants.</td></tr>
</table>

	Participants will attend a screening visit (Virtual Visit 1; Day -7). They will complete the UTI-SIQ-8 during the screening visit to assess current bothersome urinary tract symptoms. After confirming eligibility and no current symptoms, participants will be randomized to the Flush Advanced+ or placebo arm, and study product will be sent to them. At Baseline (Day 1), participants will start the 6-month use of their study product. At Baseline, participants will complete the m-RUTIIQ and PGIS. At Baseline, participants will start completing a daily diary where they will report 'good' or 'bad' urinary health days. Participants will complete the m-RUTIIQ every two weeks for the duration of the study following Baseline. They will complete the PEQ monthly (at Months 1-5), and they will complete the PGIC at Months 2 and 4. If participants have a bothersome urinary tract symptom episode while they are participating in the study, they will complete the UTI-SIQ-8, RUTISS-C, and PGIS daily for the duration of their bothersome urinary tract symptom episode. At Month 6 (EOS), participants will complete the RUTIIQ, PEQ, PGIS, and PGIC.
Statistical Methods:	Participants will be randomized in equal proportions using a secure, web-based system with permuted block randomization, and study team members will remain blinded throughout the duration of the trial. The study aims to enroll 180 participants to ensure 150 complete the study, *providing 80% power to detect a 40% difference in bothersome urinary tract symptom incidence rate over 6 months* using a significance level of $\alpha = 0.05$. Analysis populations include Safety, Full Analysis (Intention-to-Treat), and Per Protocol Sets, with outcomes assessed using survival analysis (Cox proportional hazards or similar controls), generalized linear mixed models, and appropriate parametric or non-parametric tests depending on variable type and distribution. Attention will be given to handling missing data, outliers, and confounding variables through dedicated sensitivity analyses, including modeling adherence and stratified covariates. All statistical procedures will be overseen by qualified personnel using appropriate analytical tools.
Date and Version:	May 4, 2026, V2

1.2. Schedule of Activities (SoA)

Visit	Screening Virtual Visit 1	Baseline	Active Study Period	Month 2 Check-In Virtual Visit 2	Month 4 Check-In Virtual Visit 3	End of Study Virtual Visit 4
Study Day	-7	1	1 to 168	56	112	168
Informed Consent Process	X					
Collect Demographic Data	X					
Review Medical/Health History	X	X				
Review Concomitant Medications/therapies	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Review inclusion/exclusion	X			X	X	X
Complete UTI-SIQ-8	X		X[b]			
Complete RUTISS-C			X[bc]			
Complete m-RUTIIQ		X[c]	X[c]			
Send Study Diary		X[d]	X[d]			
Send Study Product	X	X[e]				
Complete PEQ			X[f]			
Complete PGIS		X	X[b]			X
Complete PGIC				X	X	X
Monitor for recurrent bothersome urinary tract symptom episodes		X	X	X	X	X
Monitor for AEs		X[a]	X[a]	X[a]	X[a]	X[a]
Calculate Product Compliance						X

a. Concomitant medication check and AEs monitoring will be performed in the case of early termination (ET).
b. The UTI-SIQ-8 , RUTISS-C, and PGIS will be completed at the time of any bothersome urinary tract symptoms during the trial period. The UTI-SIQ-8 & RUTISS-C will be completed daily for the duration of a urinary tract symptom episode.
c. The m-RUTIIQ will be completed at Baseline and once every two weeks.
d. Study diary will be completed daily from Day 1 to Day 168.
e. Assigned study product will be consumed as instructed per group. The first dose of the study product will be consumed at Baseline.
f. The PEQ will be administered on a monthly basis from months 1-6.

1.3. Investigator and Sponsor Responsibilities

The Principal Investigator (PI) is responsible for conducting this study in compliance with the approved protocol, federal regulations, and ICH-GCP, ensuring the rights, safety, and welfare of all participants. The PI will oversee informed consent, eligibility verification, study procedures, safety assessments, data accuracy, confidentiality protections, and supervision of delegated staff. The PI will monitor adverse events, ensure proper study

product use, maintain required documentation, and promptly report deviations, unanticipated problems, and safety concerns to the Sponsor and IRB.

The Sponsor is responsible for overall study oversight, including regulatory compliance, product manufacturing and quality, provision of study materials and training, and maintaining randomization and blinding. The Sponsor will ensure secure data systems,

monitor study conduct and safety, provide medical oversight, support documentation required for IRB review, and manage participant compensation. The Sponsor affirms responsibility for data integrity, participant protection, and the ethical execution of the trial.

2. BACKGROUND AND RATIONALE:

Urologic health problems can significantly impact quality of life in women. Research suggests the effects of urologic health problems in women extend to overall well-being, social relationships, sexual relationships, and physical activity[1]. Prescription antibiotics are commonly prescribed for problems related to urologic health, and treatment and can mitigate bothersome symptoms quickly[2]. However, many women seek alternatives to prescription medications and are interested in supporting their urinary tract health using dietary supplements[3].

D-mannose is a sugar that naturally occurs within the body and is also derived from fruits and vegetables. D-mannose has been shown to be well- tolerated in humans, with clinical trials indicating no serious adverse events at doses between 2-3 g per day, though mild side effects like diarrhea may occur at higher doses, particularly above 0.2 g/kg body weight [4]. Clinical studies have supported the efficacy of D- mannose in supporting urinary tract health[5].

Urinary health may also be supported by adequate hydration[6] and the balance of key electrolytes[7], including potassium, calcium, and magnesium. Electrolytes can help maintain optimal hydration, promoting the flushing of bacteria from the urinary tract.

Vitamin C may support urinary tract health by acidifying urine, creating an environment less favorable for bacteria like *E. coli*[8]. Vitamin C may also help the body resist infection due to its role in supporting various cellular functions of the innate and adaptive immune systems[9].

Pacran® whole cranberry fruit powder has shown to significantly reduce the incidence of urologic health problems, such as urinary tract infections (UTIs), as well as and the incidence of UTI with urinary frequency and urgency symptoms[10(13)].

This clinical trial aims to evaluate the efficacy of Flush Advanced+, a dietary supplement drink mix containing D-mannose, Pacran® whole cranberry fruit powder, vitamins, and electrolytes, in improving urinary health outcomes. By targeting the mechanisms involved in UTI pathogenesis – such as bacterial adhesion and urinary pH regulation – this trial seeks to provide support for bothersome urinary tract symptom episodes that can significantly impact women's health and quality of life.

The purpose of this double-blind, placebo-controlled study is to evaluate the efficacy and safety of Flush Advanced+ in supporting urinary tract health for women aged 18-75. Flush Advanced+ is a commercially available product.

3. OBJECTIVES AND ENDPOINTS

Purpose	
The purpose of this study is to evaluate the efficacy and safety of Flush Advanced+ in supporting urinary tract health for women between the ages of 18-75	
Objectives	**Endpoints**
To determine the effect of Flush Advanced+ on bothersome urinary tract symptom episodes over the course of 6 months of use	Differences between groups in: • Total number of bothersome urinary tract symptom episodes during the 6-month study period* • Total number of sex-triggered, bothersome urinary tract symptom episodes during the 6-month study period ** • Change in total number of courses of antibiotics taken for bothersome urinary tract symptom episodes during the 6-month study period **
To determine the effect of Flush Advanced+ on overall impression of improvement over the course of 6 months of use	Intergroup and participant-level changes in individual scores across time in the change in improvement as measured by the PGIC at Baseline, Month 2, Month 4, and Month 6*

To evaluate the effect of Flush Advanced+ on urinary health outcomes after 6 months of use	Differences between groups in: • Total number of bothersome urinary tract symptom episodes during the 6-month study period * • Total number of sex-triggered, bothersome urinary tract symptom episodes during the 6-month study period** • Total number of courses of antibiotics taken for bothersome urinary tract symptom episodes during the 6-month study period** Intergroup and participant-level changes in: • Ratio of self-reported good vs. bad urinary health days assessed via daily diaries**
To determine the effect of Flush Advanced+ on sex-related quality of life (QOL)	Intergroup and participant-level changes in: • Perception of urinary health symptoms of sex life as measured by section 2 of RUTIIQ**

To determine the effect of Flush Advanced+ on urinary health-related quality of life (QOL)	• Intergroup and participant-level changes in individual scores across time in Modified Recurrent Urinary Tract Infections Impact Questionnaire (m-RUTIIQ) from Baseline to EOS**
To understand women's opinions about using the Flush Advanced+ product	• Intergroup and participant-level changes in Product Experience Questionnaire (PEQ) scores at months 1-6**
*Denotes primary endpoints of study outcome measures. **Denotes secondary endpoints of study outcome measures.	
Safety	
To assess the safety and tolerability of Flush Advanced+ in women with recurrent bothersome urinary tract symptom episodes who are otherwise healthy	Reports of adverse events (AEs)

4. STUDY DESIGN

4.1. Overall Design:

This is a double-blind, randomized, placebo-controlled, parallel-allocation clinical trial to evaluate the efficacy and safety of the Flush Advanced+ in women ages 18-75 who experience recurrent, bothersome urinary tract symptom episodes. A total of 150 women in the United States will be recruited, and each will be randomized into either the Flush Advanced+ or placebo group. Women will consume study product once daily for 6 months, and total study duration will last 6 months ± 7 days from screening until End of Study (EOS).

The study's virtual visit days include Screening (Virtual Visit 1), Month 2 Check-in (Virtual Visit 2), Month 4 Check-In (Virtual Visit 3), and EOS (Virtual Visit 4). Efficacy outcomes include total number of bothersome urinary tract symptom episodes experienced during the study, daily diary results, and scores from RUTISS-C, the m-RUTIIQ, PGIS, and PGIC. Patient experience with the product will be captured by PEQ scores. This study will be conducted virtually. The research team is located in Harrison, NY (USA).

4.1.1. Methods and Screening

Women ages 18-75 who experience recurrent, bothersome urinary tract symptom episodes will be recruited. Women must be asymptomatic at the time of enrollment, as defined by a score of 0 on the UTI-SIQ-8 questionnaire.

Recruitment for this study will be conducted in multiple ways: through HCP referrals, external recruitment platforms, Bonafide Health's internal research database, Uqora and Bonafide Health social media, and flyers.

HCPs can explain the trial to patients with recurrent, bothersome urinary tract symptom episodes histories who are being seen in-person or via telehealth. If interested, the HCP will provide the patient with the study prescreener QR code to determine their trial eligibility. Antibiotics may be administered, but participants will not be enrolled until they have finished a course of antibiotics and are experiencing no residual urinary tract symptoms.

Participants recruited via online platforms will complete an online prescreening form to determine eligibility.

The advertisement in Section
10.3.1 may be published on social media platforms affiliated with Uqora and Bonafide Health with a link to the prescreening form. They will then follow the same direction as external recruitment platform participants for enrollment.

Bonafide Health owns an internal participant recruitment database with over 20,000 women who have opted in and expressed interest in participating in clinical trials. Participants who have expressed interest or reported experiencing bothersome urinary tract symptom episodes will be recruited via text or email to complete an online prescreening form. They will then follow the same direction as external platform participants for enrollment. Regardless of recruitment method, participants will be enrolled in the trial if they are not experiencing symptoms of a current bothersome urinary tract symptom episode.

Bonafide Health operates a clinical research program consisting of trained researchers and medical oversight. Potential subjects will be recruited using Bonafide's Internal Participant database or external database access (recruitment platform) via study advertisement or email. The agreed recruitment period will start upon IRB approval and the study is expected to end in April 2027. Recruitment will occur on a rolling basis.

All women in the Bonafide Health participant recruitment database have consented to allow the research team to send them recruitment emails and questionnaires to gather information (lawful collection following appropriate privacy act mandates). Use of an external database includes women who have consented to be contacted for virtual trials on urinary health outcomes. The recruitment advertisement (see Section 10.3.1) contains information about the study, such as compensation and benefits. The information collected through questionnaires serves as a preliminary screening tool (see Section 10.2.8 for Pre-Screening Questionnaire) to isolate potential participants who may be eligible from ineligible subjects. Potentially eligible participants will be sent an electronic informed consent (eIC) to educate them about the study, and if they sign and date the form, they will be sent an electronic, countersigned copy for more details regarding the

electronic informed consent process. All eIC documents and participant materials will be stored on an internal server only accessible to the study team. Potential subjects will have ample time to read, understand, ask questions, and consult with others regarding their potential participation. Following eIC execution, the participant will then be sent the medical history questionnaire and schedule their first visit. When a participant completes the medical history questionnaire, the research team will review the responses and confirm if they are eligible based on the inclusion/exclusion criteria of the protocol.

4.2. Scientific Rationale for Study Design and Dosage

This study is designed as a randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of Flush Advanced+ in women with recurrent, bothersome urinary tract symptom episodes who are otherwise healthy. Flush Advanced+ contains Pacran® cranberry fruit powder, D-mannose, and an assortment of vitamins, and it is intended for urinary tract health support. This is the first clinical trial designed to determine the efficacy of the Flush Advanced+ product.

To ensure robust data collection, we will recruit women ages 18-75 with recurrent bothersome urinary tract symptom episodes who are otherwise healthy. This age range captures a representative population while excluding individuals with significant underlying diseases or comorbidities that could confound results or have unanticipated health reactions to D-mannose.

The 6-month supplementation period in this study requires participants to undergo daily supplementation with Flush Advanced+ or a placebo. Flush Advanced+ product is instructed to consumers to take the supplement once per day, which aligns with the Pacran® dosing recommendation. The 6-month study duration was chosen to capture the timeframe within which recurrence of symptoms can be captured; recurrent bothersome urinary tract symptom episodes may be defined as 2 or more episodes in 6 months or 3 or more within one year.

4.3. End of Study Definition

A participant is considered to have completed the study if they have completed the EOS. See Section 8.1.6 for further EOS details. Participants have the freedom to withdraw from the study at any time voluntarily (End of Study per their voluntary withdrawal date). However, if a participant is withdrawn by the investigator due to an adverse event, non-compliance, or any related issue, their last study day will be regarded as the End of Study for them.

5. STUDY POPULATION

5.1. Inclusion Criteria:

1. Healthy biological females who are 18-75 years of age (inclusive).
2. Have a body mass index (BMI) between 18.5 to 39.9 kg/m2 (inclusive).
3. Have a history of recurrent, bothersome urinary tract symptom episodes.

    a. * >5 bothersome urinary tract symptom episodes in the past 6 months OR >7 in the past 12 months will be excluded
4. Are not experiencing symptoms from a bothersome urinary tract symptom episode.
5. In good general health (no active or uncontrolled diseases or conditions) and able to consume the study product.
6. Have reliable, stable access to Wi-Fi and a smartphone/device.
7. Willing and able to agree to the requirements and restrictions of this study, willing to give voluntary consent, able to understand and read questionnaires, and able to carry out all study-related procedures.
8. English speaking.

5.2. Exclusion Criteria:

1. Individuals who are lactating, pregnant, or planning to become pregnant during the study.
2. Seeking enrollment in another clinical trial or active participation in a clinical trial.
3. Use of concomitant treatments listed in Section 10.1.12.
4. >5 bothersome urinary tract symptom episodes in the past 6 months OR >7 in the past 12 months.
5. Use of anticoagulants (e.g., warfarin) in the past 30 days.
6. Have a known sensitivity, intolerability, or allergy to any of the study products or their excipients.
7. History of hyperkalemia (high potassium).
8. History of Chronic Kidney Disease, kidney infections, or nephrolithiasis (kidney stones).
9. History of hospitalization for urologic or urinary tract symptoms.
10. History of recurrent bothersome urinary tract symptom episodes accompanied by symptoms indicative of more complications, such as recurrent fever, vomiting, chills, flank pain, visible blood in urine, and pain radiating down the legs
11. Introduction of antibiotics unrelated to a urological occurrence during the study period.
12. Current use of D-mannose.
13. Current use of cranberry supplements or cranberry juice or use of cranberry supplements of juice in 4 weeks prior to enrollment (See Section 6.5 for further details).
14. Has previously used the Flush Advanced+ product.
15. Current use of antibiotic-based prophylaxis or use of antibiotics within 2 weeks of enrollment.
16. History of Diabetes mellitus (Type 1 and/or 2).
17. Individuals who are immunocompromised, including those with known immunodeficiency disorders or receiving chronic immunosuppressive therapy (e.g., corticosteroids, chemotherapy, biologic agents).
18. History of cancer within two years prior to enrollment.
19. Use of vaginal and/or local estrogen therapy (permitted if stable dose longer than 90 days).
20. Active or suspected vaginitis.

21. Started a new nonantibiotic-based prophylaxis within the last 90 days.
22. Use of probiotics (permitted if orally administered with stable dose longer than 90 days).
23. Use of indwelling or intermittent urinary catheterization.
24. Diagnosis of overactive bladder (OAB) or interstitial cystitis / bladder pain syndrome (IC/BPS).
25. Urologic procedure within 6 months prior to trial enrollment or with a planned urological procedure in the 6 months following enrollment.
26. Any urologic or gynecologic surgical history that could cause or exacerbate urinary tract symptoms.
27. History of structural urinary tract disease or abnormalities.
28. History of Lichen sclerosis.
29. Use of potassium-sparing medications.
    a. E.g., Spironolactone (used for PCOS) (potassium-sparing diuretic); ACE inhibitors and ARBs; systemic calcineurin inhibitors.
30. Use of statins.
31. Use of Vitamin C and/or Vitamin B6 supplements as outlined in Table 6-3.

5.3. Vulnerable Populations

This study does not involve individuals who are vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons. Special classes of subjects, including students, Sponsor employees, and cognitively impaired individuals, will not be involved in this study. Individuals who are not respected as autonomous agents and/or their voluntariness is compromised will not be involved in this study.

5.4. Screen Failures

A screen failure is defined as a participant who consents to participate in the study but is not subsequently assigned to the study group. Minimal information, including Informed Consent Form (ICF) details, eligibility criteria, and demographics, will be collected.

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened, except for the cases where participants are required to meet the washout criteria for the following criteria: concomitant treatments (see Section 6.5 for further details of washout periods). A new screening number will be allocated to rescreened participants.

6. STUDY PRODUCTS

Study products are defined as any test product or placebo product intended to be administered to a study participant according to the study protocol.

6.1. Study Product Administered

Table 6-1. Study Products Administered: Flush Advanced+ or Placebo

Study Product Name	Flush Advanced+
Type	Active
Dose Formulation	One stick pack
Product Ingredients (per tablet)	Active Ingredients (Flush Advanced+): • 2 g D-mannose • 500 mg Pacran® cranberry fruit powder • 480 mg Vitamin C (as Calcium Ascorbate and Magnesium Ascorbate) • 25 mg Vitamin B6 (as Pyridoxine HCl) • 60 mg Calcium (as Calcium Ascorbate) • 12 mg Magnesium (as Magnesium Ascorbate and Magnesium Ascorbate) • 340 mg Potassium (as Potassium Citrate and Potassium Bicarbonate) Inactive ingredients: • Natural Strawberry Flavor • Citric Acid • Malic Acid • Natural Astringency Masking Flavor • Natural Raspberry Flavor • Natural Taste Modifier Flavor • Silicon Dioxide (Silica) • Xanthan Gum
	• Rebaudioside A • Natural Blueberry Flavor
Dosage Level	One stick pack once per day
Route of Administration	Oral
Dosing Instructions	• Mix one packet in 8-12 ounces of water once per day • If a dose is missed, take it later within the same day, do not double dose the next day • Take at approximately the same time every day
Sourcing/QA	Provided by sponsor; the lot was QA tested externally (Vitaquest) and is deemed safe.

Packaging and Labeling	The dosing label for both study products will contain at a minimum: • A statement indicating that it is a study product to be used for this research trial only: "For research use only" • The protocol code or identification • The name of the study product • The expiry date • Storage conditions • The name and address of the sponsor • Directions for use The Study Product labeling will be completed by Vitaquest.
Study Product Name	Placebo
Type	Placebo
Dose Formulation	One stick pack
Product Ingredients (per tablet)	<u>Active Ingredients:</u> • N/A <u>Inactive ingredients:</u> • Maltodextrin • Natural Strawberry Type Flavor • Citric Acid • Malic Acid • Natural Taste Modifier Flavor • Natural Astringency Masking Flavor • Natural Raspberry Flavor • Natural Bitter Mask Flavor • Silicon Dioxide (Silica)
	• Beet Root • Xanthan Gum • Rebaudioside A • Natural Blueberry Flavor
Dosage Level	One stick pack once per day
Route of Administration	Oral
Dosing Instructions	• Mix one packet in 8-12 ounces of water once per day • If a dose is missed, take it later within the same day, do not double dose the next day • Take at approximately the same time every day

Sourcing/QA	Provided by sponsor; the lot was QA tested externally (Vitaquest) and is deemed safe.
Packaging and Labeling	The dosing label for both study products will contain at a minimum: • A statement indicating that it is a study product to be used for this research trial only: "For research use only" • The protocol code or identification • The name of the study product • The expiry date • Storage conditions • The name and address of the sponsor • Directions for use The Study Product labeling will be completed by Vitaquest.

6.2. Study Product Preparation, Handling, Storage and Accountability:

1. The study product is stable for storage between 55-75 °F, 30-50% humidity, and away from direct sunlight.
2. The primary investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study products received and that any discrepancies are reported and resolved before use of the study products.
3. Only participants enrolled in the study may receive the study product, and only authorized personnel may supply or administer study products. A product dispensing log will be maintained.
4. The principal investigator is responsible for the study product accountability, reconciliation, and record maintenance (i.e., receipt and reconciliation).
5. Any returned study product will not be re-dispensed to other participants.

6.3. Measures to Minimize Bias

Table 6-2 Methods to Minimize Bias and Their Description

Method to Minimize Bias	Description
Randomized, Double-blind, Placebo-controlled Study Design	This is a double-blind, randomized, placebo-controlled parallel allocation study. Both the participant and the study personnel (i.e., sponsor representative involved in the study, the investigator, study team, data management, statisticians, and any health care professionals or other site personnel involved in participant management or outcome assessment) will not be aware of which study product (Flush Advanced+ vs placebo) participants receive throughout the full duration of the study.
Randomization	In the 1:1 ratio, participants will be randomly assigned to receive either Flush Advanced+ or placebo for the full duration of the intervention period. Study products will be dispensed as per the randomization scheme at the study visits summarized in the SoA (1.2). Randomization numbers will be associated with the allocation to study products.

6.4. Study Product Compliance

Participants will consume the first dose of the study product at Baseline and self-administer at home for the remainder of the study period. Compliance will be assessed by participants counting the remaining study product and by study diary data. Compliance will be documented as part of the participant's data collection file. At the End of Study, participants may dispose of any unconsumed study products remaining as well as empty packaging. Any non-compliance in the administration of the study product will be documented as a protocol deviation.

In the event of a discrepancy between the counted study product and the self-reported information recorded in the diary, participants will be instructed to ship and return unused product for the research team to count and determine compliance unless an explanation for loss of product has been provided. Compliance calculations will be performed by the principal investigator and research members. Compliance over the dosing period will be calculated by dividing the amount of study product ingested by the amount of study product expected to have been ingested and then multiplying by 100. A compliance of 80% or greater is deemed compliant.

6.5. Concomitant Treatments

See Table 6-3 below for a full list of restricted concomitant treatments for the study. Use of these treatments in the defined timeframe may lead to screen failure or early termination of the participant.

Table 6-3. Restricted concomitant treatments throughout the study (unless otherwise stated)

Type of treatments	Items
Prescribed and over-the-counter medications	• Potassium-sparing or wasting medications (E.g., Spironolactone, ACE inhibitors, ARBs, and calcineurin inhibitors) • Statins • Antibiotic-based prophylaxis* • Anticoagulant medications** *Participants must not be currently taking antibiotics at the time of their Baseline Visit, and they must not have taken any antibiotics in the 2 weeks prior to their Baseline Visit. Antibiotics may be taken if prescribed for urinary tract symptoms during the duration of the study thereafter. **Participants must not be currently taking anticoagulants and must not have taken any anticoagulants in the 30 days preceding enrollment.
Supplements/foods/drinks	Oral supplements used for urinary or general health: • D-mannose* • Cranberry extract, supplements, or juice** • Methenamine*** • Probiotics*** • Vitamin C**** • Vitamin B6**** * Use during the trial period is not permitted. **Use of cranberry supplements or cranberry juice during the trial period is not permitted. Participants may complete a 30-day washout period to be enrolled in the trial. *** Permitted if a stable dose has been used for 90 days and is maintained for the duration of the study; start or stop of usage or changing dosage during the study may lead to early termination. Participants may complete a 30-day washout period to be enrolled into the trial. ****Use during the trial is not permitted only if the total daily amount consumed (including the amount in Flush Advanced+) meets or surpasses the tolerable upper intake levels (ULs) for adult females, per NIH guidelines - The UL for Vitamin C for adult females is 2,000 mg - The UL for Vitamin B6 for adult females is 100 mg

Therapies	• Vaginal or local estrogen* • Spermicide use (contraceptive methods)*

	• Indwelling or intermittent urinary catheterization * Permitted if a stable dose has been used for 90 days and is maintained for the duration of the study; start or stop of usage or changing dosage during the study may lead to early termination.

Any other medication or vaccine (including over the counter or prescription medication, vitamins, and/or supplements) that the participant is receiving at the time of screening or receives during the study must be recorded along with:

1. Reason for use
2. Dates of administration, including start date, and if applicable, end date
3. Dosage information, including dose and frequency

7. DISCONTINUATION OF STUDY PRODUCTS AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Products

Participants may need to permanently discontinue (definitive discontinuation) consuming the study product in rare instances. If the study product is definitively discontinued, the participant will not remain in the study to be evaluated, but the data collected thus far will be included for analysis.

7.2. Participant Discontinuation/Withdrawal from the Study

After confirming the eligibility for the study, a participant may withdraw from the study at any time at their request, irrespective of the reason. A participant may also be withdrawn at any time at the discretion of the principal investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon. The principal investigator must permanently discontinue study product use and withdraw a participant for the following reasons:

- The participant had a study product-related serious adverse event (SAE)
- Death
- Significant protocol deviation, withdrawal as determined by the investigator
- Significant study product non-compliance
- Pregnancy
- Participant lost to follow-up
- All study withdrawals will be recorded by the principal investigator and/or research members on the appropriate source documents when considered confirmed. The reasons for withdrawals should be labeled with the terms below:
- Adverse event
- Failure to return (lost to follow-up)
- Other medical event
- Other non-medical event
- Protocol deviation

- Participant request for withdrawal

A participant's decision to withdraw will not cause the loss of any benefits to which they are entitled.

- At the time of discontinuing the study, if possible, an early termination, virtual visit will be conducted.
- The participant will be permanently discontinued from the study product and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Bonafide will send each participant a box with a return shipping label so that the remaining supplement can be shipped back following the virtual withdrawal visit (this box and label will be available to participants upon the first shipment from Bonafide). If the participant's supplement does not arrive back to the office within 7 days, a member of the research team will reach out to the participant to discuss, alternatively, destroying the supplement.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the research team.

The following actions must be taken if a participant fails to attend a required virtual/telephone visit:

- The research team must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the research team must make every effort to regain contact with the participant (where possible, 3 virtual visits and/or telephone calls separated by 24 hours). These contact attempts should be documented in the participant's study record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with lost to follow-up as the primary reason.

Participants may be contacted throughout the study period to remind them of their upcoming study procedures as a means of maximizing participant retention. Automated reminders may be made via text messages, telephone and/or email, if necessary.

8. STUDY ASSESSMENTS AND PROCEDURES

- Immediate safety concerns should be discussed with the principal investigator by members of the research team or participants themselves upon occurrence

or awareness to determine if the participant should continue or discontinue the study product. The PI will consult the Medical Expert in all instances.

- Adherence to the study design requirements, including those specified in the SoA (Section 1.2), is essential and required for study conduct. Protocol waivers or exemptions are not allowed.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The research team will maintain a screening log (see Section 10.3.2) to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Data will be collected electronically via the secure JotForm and/or Form Assembly platform with encryption. Only IRB approved research team members will have access to data collection forms and JotForm/Form Assembly surveys.
- Virtual visits will be conducted via phone call or Microsoft Teams.
- Participants will be compensated for their time (details may be found in the compensation Section 8.3).

8.1. Narrative of Study Procedures

8.1.1. Screening (Virtual Visit 1; Day -7)

Following initial prescreening to determine initially eligible participants, those who are initially eligible will receive the electronic Informed Consent Form (eICF) to review and complete. The signed and dated eICF from the eligible participant (see recruitment section below) will be collected prior to the screening visit. Participants recruited for this research or who are interested in the study will be sent the eICF via Form Assembly. Prior to signing, participants will have the ability to speak with a research team member or talk to their personal doctors or others they wish to ask about the study and requirements. Once an electronic copy (signed by participant and research team) of the informed consent has been sent back from the participant, they will then be routed to complete the Medical History Questionnaire (MHQ), also on Form Assembly. Once the MHQ is complete, they will be able to schedule a screening visit with a study team member. A member of the research team will review and confirm the participants full eligibility and, if eligible, complete Virtual Visit 1 with the participant. If the participant is deemed ineligible following the submission of their MHQ, a research team member will notify the participant and cancel their scheduled Screening visit.

The screening visit (Virtual Visit 1) will be a 1-on-1 call through Microsoft Teams or phone call. Participants will meet directly with a research investigator and will be able to verbally ask questions. During the screening visit, participants will need to provide valid identification (i.e., driver's license, government-issued passport, or birth certificate) on camera at the beginning of this visit to verify their identity. If the participant elects not to participate or is unable to provide a valid form of identification during the visit, the study team member will reschedule the visit or remove the participant from the study.

<u>The following information will be recorded and procedures carried out:</u>

- Confirm identity
- Collect demographic data (age, ethnicity, race, etc.)
- Review medical/health history
- Review/record use of concomitant treatments and medications
- Collect information about bothersome urinary tract symptoms and history
- Collect lifestyle information (alcohol consumption, exercise, sexual activity)
- Review inclusion/exclusion criteria
- Confirm personal information required to participate (phone number, address)

If eligible, the participant will be officially enrolled in the study and the following procedures will be carried out:

- Explain the purpose and how to conduct study diaries and questionnaires
- Send the UTI-SIQ-8 through the JotForm platform
- Explain compensation
- Send study product to eligible participants

8.1.2. Baseline (Day 1)

Participants will be instructed to begin consuming their study product once per day. There will not be a virtual visit for Baseline (Day 1). Baseline marks the start of the intervention period. Participants will begin completing daily diaries on this day to track compliance, changes in health, good/bad urinary health days, and any bothersome urinary tract symptoms they experience. Participants will also complete the m-RUTIIQ and PGIS for the first time on Day 1.

8.1.3. Biweekly Check-In Messages

To maintain participant engagement, collect urinary health-related quality of life information, and promote study compliance, participants will receive a check-in message once every two weeks. The message will contain a link to a JotForm with the m-RUTIIQ to complete. The form will also include a text box they can use to ask any questions or voice concerns to the research team.

8.1.4. Month 2 and Month 4 Check-In Visits (Virtual Visits 2 & 3; Day 56 & 112)

The second and third virtual visit will take place at Months 2 and 4. Each visit will last approximately 15 minutes.

The following information will be recorded, and procedures will be carried out:

- Review changes in concomitant treatments, medications and therapies
- Review inclusion/exclusion criteria
- Review and document Adverse Events
- Remind participants of instructions when they experience bothersome urinary tract symptoms.
- Participants will complete the PGIC and PEQ before or at Month 2 and Month 4 Check-Ins

8.1.5. Interim Check-In Texts (Unscheduled: In the event of a bothersome urinary tract symptom episode)

The following information will be recorded, and procedures carried out when a participant experiences bothersome urinary tract symptoms:

- Notify the research team
- Notify HCP, if applicable
- Participants will be instructed to complete the UTI-SIQ-8, RUTISS-C, and PGIS via JotForm
- Review changes in concomitant treatments, medications and therapies
- Review and document Adverse Events
- Remind the participants of all study requirements

8.1.6. End of Study (Virtual Visit 4; Day 168)

The End of Study virtual visit will take place 6 months after Baseline. This visit will last approximately 15 minutes.

The following information will be recorded, and procedures will be carried out:

- Review changes in concomitant treatments, medications and therapies
- Review inclusion/exclusion criteria
- Review and document Adverse Events
- Calculate study compliance
- Participants will have completed the required questionnaires before conducting the visit. The questionnaires included are: m-RUTIIQ, PGIS, PGIC, and PEQ.
- Research members will confirm questionnaires have been completed. If they have not been completed, they will be asked to complete these electronic questionnaires (JotForm) during the visit.

8.1.7. Early Termination / Discontinuation Visit

In case of early termination, the following information will be recorded, see details in SoA (Section 1.2):

- Review the study diary to assess changes in concomitant treatments and changes in health/AEs.
- Participant will be instructed on discarding unused study product.

8.2. Efficacy Assessments

8.2.1. Total number of courses of antibiotics taken for episodes of bothersome urinary tract symptoms.

A secondary outcome is the total number of courses of antibiotics taken when a participant experiences bothersome urinary tract symptoms during the study period. Following Baseline through EOS, the total number of days on antibiotics will be calculated. When participants are administered active questionnaires, they will also be asked to provide information regarding new antibiotic treatment (e.g., name, dose, route of administration).

8.2.2. UTI-SIQ-8

The Urinary Tract Infection-Symptom and Impairment Questionnaire (UTI-SIQ-8) is a questionnaire that assesses the current severity of and level of impairment due to dysuria, urinary urgency, urinary frequency, and low abdominal pain[15]. Each of the four questions about symptom severity is answered on a 5-point Likert scale of 0-4, with 0 representing 'not at all' and 4 representing 'very strong'; each of the four questions about impairment is also answered on a 5-point Likert scale of 0-4, with 0 representing 'not at all' and 4 representing 'very severe'. All participants will complete the UTI-SIQ-8 at Screening and each time they experience bothersome urinary tract symptoms during the 6-month study duration. When participants report experiencing bothersome urinary tract symptoms during the study period, they will the UTI-SIQ-8 once daily for one week. More details and a copy of the UTI-SIQ-8 can be found in Section 10.2.1.

8.2.3. RUTISS-C

The Recurrent Urinary Tract Symptom Scale is a validated patient-reported outcome measure that assesses the symptom burden and quality of life associated with recurrent bothersome urinary tract symptoms. We will only be administering and collecting data from Section C of the RUTISS based on its relevance to the study's primary objectives, which center on patient-reported impacts of recurrent bothersome urinary tract symptoms on daily functioning and quality of life. All participants will complete the RUTISS-C each time they experience a bothersome urinary tract symptom episode during the 6-month study duration. When participants report bothersome urinary tract symptom episodes during the study period, they will complete the RUTISS-C once daily until their symptoms resolve. More details and a copy of the RUTISS-C can be found in Section 10.2.2.

8.2.4. Modified RUTIIQ

The Modified Recurrent Urinary Tract Infection Impact Questionnaire (m-RUTIIQ) is a validated measure evaluating the self-reported burden of urinary tract symptoms on quality of life and health. Each of the items on the questionnaire addresses urinary tract symptoms' impact on at least one of the following areas: personal and/or social well-being, work and activity interference, satisfaction with urinary tract-related care, and sexual well-being. Participants will complete this questionnaire at Baseline and every two weeks thereafter until the End of Study (EOS) visit. More details and a copy of the m-RUTIIQ

can be found in Section 10.2.3.

8.2.5. Good Urinary Health Days

Participants will keep a record of self-reported "good urinary health days" in their daily diaries. In each daily entry they will be asked to rank the day as either "good" or "bad". Participants will begin daily diary entries at Baseline and continue each day throughout the duration of the study, with the last entry logged at End of Study. The format of this question can be found in Section 10.2.4.

8.2.6. PGIS

The Patient Global Impression of Severity (PGIS) scale assesses participants' self-reported level of current symptom severity. The PGIS includes one question answered on a 7-point Likert scale, where 1 represents 'not present' and 7 represents 'extremely severe'. Participants will complete this scale at Baseline and EOS. More details and a copy of the PGIS can be found in Section 10.2.5.

8.2.7. PGIC

The Patient Global Impression of Change (PGIC) scale assesses participants' self-reported level of improvement at the end of the study compared with their status at the beginning of the study. The PGIC includes one question answered on a 7-point Likert scale, where 1 represents 'very much improved' and 7 represents 'very much worse'. Participants will complete this scale at Month 2, Month 4, and Month 6 (EOS visit) timepoints. More details and a copy of the PGIC can be found in Section 10.2.6.

8.2.8. PEQ

A product experience questionnaire (PEQ) will be used to determine participant satisfaction with the Flush Advanced+ product on a monthly basis (Months 1-6). More details and a copy can be found in Section 10.2.7.

8.2.9. Prescreener Questionnaire

A subject prescreener questionnaire will be used to determine participant eligibility based on their selected responses. This will be administered during the prescreening phase of the study. More details and a copy can be found in Section 10.2.8.

8.3 Compensation

Participants will receive varying compensation amounts depending on the completion of the trial procedures:

- Screening Visit: $75.00
- Bi-Weekly Questionnaire: $72.00 ($6.00 per response)
- Monthly Questionnaires: $60.00 ($10.00 per response)
- Month 2 Visit: $75.00
- Month 4 Visit: $75.00
- End of Study Visit: $75.00

- Daily Diaries: $168.00 ($1.00 per diary for 168 days)

Total Possible: $600.00

Compensation will be paid after the Screening visit and after each bimonthly visit (Month 2, Month 4, and Month 6). If a participant withdraws from the study at any point, the participant will receive their compensation for the trial procedures completed from the last time point.

8.4. Compensation for Research-Related Injury

No commitment is made by Bonafide Health or its parent company, Pharmavite (collectively referred to as the Sponsor and Institution), to provide free medical care or financial compensation for injuries sustained by participants in this study. If a participant experiences an injury or illness as a result of their participation in this study, reimbursement for related medical costs will be sought from their insurer, managed care plan, or other benefits program. Participants with insurance may be responsible for any associated costs, including co-payments and deductibles, as required by their insurance policy. It is important that you inform the investigator(s) immediately if you experience an injury or illness due to participation in this study. To process medical expense payments, the sponsor may need certain information from you, such as your name, date of birth, and Medicare Beneficiary Identifier (MBI). If you are a Medicare recipient, the sponsor is required to report any payments made on your behalf to Medicare.

8.5. Safety Assessments

8.5.1. Adverse Events and Serious Adverse Events

An AE is any undesirable or unanticipated occurrence that may present in patients participating in research studies even if the event is not considered to be related to the study product (SP). An SAE is considered any undesirable sign, symptom, or medical condition with one or more of the following outcomes:

- Death of any of the participants associated with the research study
- An event that can lead to life-threatening complications or use of the study product might have resulted in the death of the participant
- Events that may lead to immediate admission to the hospital or prolonged hospitalization
- Events that result in permanent or temporary physical disability/incapacity that affect the participant's body function/structure, physical activities and/or quality of life
- Events that lead to any type of congenital abnormalities or birth defects
- Events that lead to medical or surgical intervention required to prevent permanent impairment or damage due to the suspected use of the study product
- Events that do not fit the other outcomes but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other

outcomes

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The principal investigator and research members are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs per Section 8.5.1.3.

All SAEs (and their follow-ups) should be captured on an SAE form and emailed within 24 hours to tvandusseldorp@bonafidehealth.com. The principal investigator will then notify the medical expert (Dr. Alyssa Dweck) within 24 hours of receipt. The PI will also notify the IRB within 24 hours of the original receipt.

Reported outcome questionnaires will not be reviewed for potential AEs. Only reported or observed changes in health will be reviewed for potential AEs.

8.5.1.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the first dose of the study product (Baseline) until EOS (Virtual Visit 4) and reviewed at the visits and interim follow-ups specified in the SoA (Section 1.2).

Medical occurrences that begin before taking the study product but occur after obtaining informed consent or occur after taking the study product with previous history will be recorded on the Medical History/Current Medical Conditions questionnaire. Only medical occurrences that begin or exacerbate after taking the study product will be reported as AEs/SAEs.

The research team is not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the research team learns of any SAEs, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the study product or study participation, the research team must promptly notify Trisha VanDusseldorp, PhD. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.5.1.2. Method of Detecting AEs and SAEs

Safety and adverse events (e.g., GI distress, headaches) will be collected from participant diaries or in the event there is an adverse event that a participant contacts the study team directly (see section 8.5.1 for details on capturing SAEs and AEs 8.5.1). Additionally, subjects will be asked about any changes in health via daily diaries and at Virtual Visits 2, 3, and 4, which take place at Months 2, 4, and 6, respectively.

8.5.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the principal investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as

defined in Section 7.3). Further information on follow-up procedures is provided by the sponsor's SOP.

8.5.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification of an SAE by the principal investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study product under clinical investigation are met.

The sponsor has a legal responsibility to notify the local regulatory authority, other regulatory agencies, and other investigators researching the same study product, per regulation, about the safety of a study product under clinical investigation. This can be done by the sponsor or the principal investigator. Further information on regulatory reporting requirements for SAEs is provided by the sponsor's SOP.

8.5.1.5. Pregnancy

While pregnancy itself is not considered to be an AE or SAE, abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered AEs or SAEs.

Any pregnancy for enrolled participants will be reported if it occurred during the time from the first dose of study product until the EOS visit. Pregnancies of partners of enrolled participants should also be reported if occurred during the time from the participant's first dose of study product until the EOS visit.

If a pregnancy is reported, the principal investigator will report it to the sponsor and IRB as appropriate. Pregnant participants will be withdrawn from the study and pregnancy will be followed to resolution.

9. STATISTICAL PLAN

9.2. Group definitions

This study has 2 arms:

- **P** = placebo sachet
- **T_1** = treatment with one sachet of Flush Advanced+ drink mix every day for 180 days.

9.3. Randomization and Concealment

This is a double-blinded, parallel-group, randomized, placebo-controlled trial with a 1:1 allocation ratio.

Randomization will be performed using a secure web-based randomization system. Study site staff will access the system only after confirming participant eligibility and completing the baseline assessment.

Computer-generated permuted block randomization will be used to maintain allocation

balance at regular intervals. Each block will contain 2 assignment slots, with 1 participant assigned to each arm within the block.

Study team members, outcome assessors, and data analysts will be blinded to treatment allocation where feasible.

9.4. Sample Size Determination

A total of 180 participants will be enrolled to ensure that at least 150 complete the study, allowing for an estimated 20% attrition due to concomitant medication use or other life circumstances that may interfere with participation. While we do not anticipate a dropout rate of this magnitude, the target sample size provides a buffer to maintain adequate statistical power.

Based on prior trials (Hayward 2024; Domenici 2016; Kranjčec 2014), the expected median time to bothersome urinary tract symptoms is approximately 90 days. The median treatment effect observed in similar interventions was a 40% prolongation in time to recurrence. The proposed sample size provides 80% power to detect a 40% difference in hazard rates between treatment groups (active vs placebo) using a two-sided $\alpha = 0.05$.

The research team will devote the necessary time to recruiting the specified number of participants in the agreed recruitment period. Recruitment methods are discussed in more detail in Section 4.1.1.

9.5. Analysis Sets

The following analysis sets are defined:

Population	Description
Safety Set (SAF)	The safety population will include all randomized participants who received at least one dose of study product. The safety population will be used in the analysis of all safety endpoints.
Full Analysis Set (FAS) aka Intention to Treat (ITT)	The FAS is the subset of the SAF who also have • Data from the baseline visit AND • Data from at least one post-baseline visit The FAS population will be used as for intention to treat analysis of efficacy.
Per Protocol Set (PPS)	The PPS is the subset of FAS that excludes participants with major protocol deviations, including but not limited to the following: • Retrospective discovery of ineligibility • Missing primary outcome data • Overall computed compliance of ≤80% or ≥120% of dispensed study product • Use of restricted concomitant treatments defined in Table 6-3 • Reassignment to a different group than originally randomized • Death, loss to follow-up, or withdrawal from the study The PPS population will be used for per-protocol analysis of efficacy as well as secondary sensitivity analyses.
Sub-Group Analysis: Sex-Triggered bothersome urinary tract symptoms	This Sub-Group Analysis is the subset of the SAF who • Reported in the prescreening form that 'sexual activity' is a 'primary' or 'additional' trigger of bothersome urinary tract symptoms This population will be used for analysis of efficacy.

9.6. Descriptive Statistics

Descriptive statistics will be employed to summarize and characterize the study variables.

- For binary and categorical variables: N, frequencies and corresponding percentages will be reported in tabular form.
- For continuous variables: Appropriate summary measures will be presented depending on the distribution of the data. Normally distributed continuous variables will be described using means and standard deviations (SD). Non-normally distributed variables will be summarized using medians along with the first (25th percentile) and third (75th percentile) quartiles. In addition, the range, including minimum and maximum values, will be provided for all continuous variables to convey the data spread.

9.7. Statistical Methods

All statistical analyses will be performed using SPSS (Version 31) or comparable statistical software. Descriptive statistics (mean, standard deviation, median, interquartile range, frequency, and percentage) will summarize baseline characteristics and outcomes. A significance level of $p < 0.05$ (two-sided) will be used for all inferential tests.

Primary and Secondary Efficacy Analyses

For the primary and secondary efficacy endpoints, differences between groups (Flush Advanced+ and placebo groups) of the total number of sex-triggered bothersome urinary tract symptoms, and courses of antibiotics taken during the 6-month study period will be analyzed using generalized linear mixed models (GLMM) with a negative binomial distribution to account for count data and repeated measures within participants. Treatment group, study period (pre-study vs. on-study), and their interaction will be included as fixed effects.

Continuous or ordinal questionnaire outcomes (e.g., m-RUTIIQ, PGIC, RUTIIQ Section 2) will be analyzed using mixed-effects models or nonparametric tests (e.g., Wilcoxon rank-sum) depending on data distribution. The ratio of “good” to “bad” urinary-health days from daily diaries will be summarized as proportions and compared between groups using a logistic mixed-effects model.

A subgroup analysis will be performed among participants with sex-triggered bothersome urinary tract symptoms (those reporting at baseline), using the same models as the primary analysis but limited to this subgroup. An interaction term between treatment and subgroup (sex-triggered vs. non–sex-triggered) will be explored to assess differential treatment effects.

Other analyses may be implemented accordingly.

9.8. Missing Data

Data is assumed to be Missing at Random (MAR) unless evidence suggests otherwise. All randomized participants will be accounted for at each stage of the study, and a summary flowchart will report the number and percentage of participants randomized, excluded (with reasons), withdrawn, lost to follow-up, and who completed each assessment, by treatment group and time point.

To assess the validity of the MAR assumption, we will compare baseline characteristics between participants with and without complete primary outcome data. Logistic regression models will be used to evaluate whether any baseline covariates are associated with missingness; odds ratios, 95% confidence intervals, and p-values will be reported.

For the time-to-event outcome (time to first recurrence), censoring will be handled using standard survival analysis techniques. Censoring rules are described in 8.2.1. Missing data due to loss to follow-up is censored at the date of last interaction with the research team.

For the secondary endpoint analysis of recurrent bothersome urinary tract symptoms (binary outcome), the generalized linear mixed model inherently accommodates missing data under the MAR assumption.

9.9. Outliers

Outliers will be systematically identified and evaluated for the primary outcome, time to first recurrent bothersome urinary tract symptoms, a continuous variable. In this dataset, outliers are defined using the following criteria:

- Categorical variables: Value > Quartile [75] + 1.5 x IQR or Value < Quartile [25] - 1.5 x IQR
- Continuous variables: Value z-score ≥3

All potential outliers will be carefully reviewed to determine whether they represent true clinical events or arise from data entry errors, measurement mistakes, or protocol deviations.

Sensitivity analyses will be conducted to evaluate the impact of outliers on the primary and secondary outcomes. This will include separate analyses for censoring, retaining, or winsorizing the outliers to the nearest threshold.

9.10. Predefined Sensitivity Analysis

The Per Protocol Set (PPS) provides a sensitivity analysis of treatment effects among participants who were optimally compliant, had no major protocol deviations, and had minimal missing data. In addition, dedicated sensitivity analyses will be performed to assess:

1. The impact of missing data: Models may be re-run with baseline covariates associated with missingness included as adjustment variables. Sensitivity under the MAR assumption will explored using worst-case/best-case imputation scenarios. If missingness is extensive or potentially not at random (MNAR), multiple imputation will be used, and the imputed results will be compared to complete-case analyses.

2. The impact of treatment adherence: Adherence will be modeled as a continuous variable and included in Cox proportional hazards regression to evaluate for a potential dose-compliance relationship. In addition, we will perform compliance average caused effect (CACE) analysis. This allows the theoretical effectiveness of Flush Advanced+ to be modeled in participants who exhibit adequate adherence. Adequate adherence is defined as taking ≥70% or of Flush Advanced+ doses at the intended time. Note: this is a patient-reported metric that differs from end-of-study computed global compliance.
3. The impact of confounding variables: Potential confounders will be stratified as follows:
    - Menopausal status: [Pre], [Peri] or [Post]
    - Number of bothersome urinary tract symptom episodes in last year: [2-4] and [5-7]
    - Time between resolution of previous urinary tract symptoms and initiation of study product: [≤60 days, [60-90 days], or [>90 days]
    - Self-report of sex as the primary trigger for bothersome urinary tract symptoms: [yes] or [no]
4. Because several of these confounders are covariant (e.g. age x menopause), sensitivity analysis will be stratified on each variable individually rather than constructing a fully adjusted proportional hazard model.

9.11. Personnel and Equipment

All calculations and analyses will be supervised by a clinical trialist with advanced training in biostatistics. Analyses will be performed and data visualized using SPSS (version 31), PRISM GraphPad 9 (version 10) or equivalent software.

9.12. Safety Analysis

Safety analyses will be conducted on the safety population and summarized by the treatment group. Treatment-emergent adverse events (TEAEs) will be summarized by body system, severity, or relationship to the study product for each treatment group and time point. For the counts of participants with a TEAE, each participant may only contribute once to the incidence rates for a specific TEAE, regardless of the number of occurrences. Serious adverse events (SAEs) will be presented separately, stratified by treatment group and time point

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.2. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.2.9. Regulatory and Ethical Considerations

10.2.9.1. This study will be conducted in accordance with the protocol and the following:

10.2.9.1.1. Applicable ICH GCP Guidelines

10.2.9.1.2. Applicable laws and regulations

10.2.9.2. The protocol, protocol amendments, ICF, ICF amendments, and other relevant documents (e.g., recruitment material and participant material) will be submitted to an IRB by the principal investigator or designated personnel from the research team and reviewed and approved by the IRB before the study is initiated.

10.2.9.3. Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

10.2.9.4. The principal investigator or designated research member(s) will be responsible for the following:

10.2.9.4.1. Providing written summaries of the status of the study to the IRB in accordance with the requirements, policies, and procedures established by the IRB

10.2.9.4.2. Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures

10.2.9.4.3. Providing oversight of the conduct of the study at Bonafide and adherence to requirements of ICH guidelines, the IRB, and all other applicable regulations

10.2.9.5. The sponsor or a delegate is responsible for the submission of applicable SAEs and safety information to the Health Regulatory Agencies and other investigators.

10.2.10. Sponsorship Disclosure

All the study products, study procedures, and other requirements as part of this study are paid for by the study sponsor and provided at no cost to the participant, their public health plans, or the participants' private medical insurance. Participants will be reimbursed by the sponsor for any reasonable medical expenses for treatment of any adverse reaction to the study product, if both the investigator and the sponsor agree that the adverse reaction was caused from proper use of the study product as outlined in the protocol for the study. The participants' public health plans or personal medical insurance (if any) will continue to

pay for expenses for their current medical care and/or prescriptions. These expenses will not be paid as part of the participants' participation in this study.

The study is fully financed by Bonafide Health. No members of the research team receive financial compensation related to the outcomes of this study or own stock or related in Bonafide Health.

10.2.11. Informed Consent Process

10.2.11.1. The principal investigator or research member will explain the nature of the study to the participant and answer all questions regarding the study (virtual/telephone). The research team will devote the necessary time required to answer all questions the potential participant may have regarding the study. The potential participant will be encouraged to speak with family, friends, and their primary care physician.

10.2.11.2. Participants will be informed that their participation is voluntary. If the participant agrees to participate in the study, they will be required to sign an ICF that meets the requirements of local regulations, ICH guidelines, Personal Information Protection and Electronic Documents Act requirements, where applicable, and the IRB or study center.

10.2.11.3. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study (if applicable).

10.2.11.4. An electronic copy of the ICF(s) will be provided to the participant.

10.2.11.5. In case of an injury or illness suffered by participation in this study, participants will receive appropriate medical care. By signing the ICF, participants do not give up their legal rights nor release the study doctor or sponsor from their legal and professional obligations.

10.2.11.6. Participants may discontinue participating at any time without penalty or loss of benefits to which they are otherwise entitled.

10.2.12. Data Protection

10.2.12.1. Data will be collected electronically via the secure Form Assembly platform with encryption, which is HIPAA-compliant. Only IRB approved research team members will have access to data collection forms and Form Assembly surveys.

10.2.12.2. Data will also be collected electronically via the secure and HIPAA-compliant JotForm platform. Only IRB approved research team members will have access to data collection forms and JotForm questionnaires.

10.2.12.3. Participant's data will be deidentified using a participant coding system that will not identify the participant with their research study data. For example, the first participant enrolled would be deemed BH-FADV-001.

10.2.12.4. Participant's data will be identified to IRB approved research team members in the case of an AE or SAE to ensure participants safety.

10.2.12.5. The participants will be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of

disclosure must also be explained to the participant, who will be required to give consent for their data to be used as described in the informed consent.

10.2.12.6. The participants will be informed that their medical records/source documents may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.2.13. Data Quality Assurance

10.2.13.1. Participant data relating to the study will be imported from the JotForm and/or Form Assembly platform into a password protected Microsoft Excel sheet stored on the secure Bonafide Server.

10.2.13.2. The principal investigator and research team must maintain accurate documentation (source data) that supports the information entered and stored electronically. Study records stored electronically will be password protected (word, PDF, excel) documents stored on the secure Bonafide Server. Only IRB approved research team members will have access to these files.

10.2.13.3. The principal investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

10.2.13.4. Monitoring will be performed by the principal investigator and medical expert to ensure adherence to the study procedures and to ensure that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements and that the safety and rights of participants are being protected.

10.2.13.5. The research team will be responsible for the data management of this study, including quality check and cleaning of the data.

10.2.13.6. The sponsor assumes full accountability by having proper control and oversight of the responsibilities delegated to other individuals (e.g., research members).

10.2.13.7. Records and documents including signed ICF(s) and data collection forms, pertaining to the conduct of this study must be retained by the sponsor on the secure Bonafide Server for at least seven (7) years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.2.14. Protocol Deviations

A protocol deviation (PD) is a deviation from the protocol that occurs in conduct of the study (criteria, procedure, or protocol requirements). Impacts of each PD on participant safety will be classified as either major or minor. All PDs with a major impact will be identified and reviewed by members of the research team within 24 hours of their discovery, and the principal investigator will determine if a quality issue should be reported to the sponsor and IRB and informed as appropriate.

Using the data entry system and source documents, it is the responsibility of the research team to use continuous vigilance to identify and report PDs to the principal investigator. The principal investigator will review the PDs, and the major PDs will be reported to the sponsor if appropriate.

All protocol deviations must be documented by the research members in the password protected Microsoft Excel sheet stored on the secure Bonafide Server.

10.2.15. Source Documents

All required documents (e.g., daily diaries, questionnaires, scales, etc.) will be electronic documents created on JotForm's platform and completed virtually by participants. Research members will transfer the encrypted, completed data into the password protected Microsoft Excel sheet stored on the secure Bonafide Server.

The medical history questionnaire and informed consent will be created on Form Assembly's platform and collected in a HIPAA compliant manner. This data will be deidentified and transferred to be stored securely on the Bonafide Server. Only IRB approved research team members will have access to data collection forms and Form Assembly surveys.

10.2.16. Study Start and Completion

The study start date will be the date of the first participant screened. The sponsor or sponsor designee reserves the right to terminate the study at any time for any reason at the sole discretion of the sponsor. The study is considered completed at the last study visit for the last participant. In the event that the last participant is deemed lost to follow-up by being unreachable after the follow-up attempts (see Section 7.37.3) the study will be considered complete.

10.2.17. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination will be provided by the principal investigator to study participants and the sponsor as applicable. If the study is prematurely terminated or suspended, the principal investigator will promptly inform study participants, the IRB, and sponsor as applicable and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule. The IRB will be notified of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

10.2.17.1. Determination of unexpected, significant, or unacceptable risks to participants
10.2.17.2. Insufficient compliance to protocol requirements
10.2.17.3. Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor and/or the IRB.

10.2.18. Potential Benefits to Subjects

Participation in this research does not guarantee benefits to the participants, as the study team cannot guarantee urinary health-related outcomes will improve. Results from this research will provide the benefit of enhancing the knowledge about the efficacy of the study product, a natural dietary supplement, on urinary health-related outcomes.

10.2.19. Economic Burden to Subjects

There are no direct costs other than the participant's time. The study product and required materials will be given to the participants at no charge.

10.2.20. Risks to Subjects

There are risks of emotional distress, inconvenience, and possible loss of privacy and confidentiality when participating in a research study. However, the research team will take every action to keep the participant's personal information and data private, but this is always a risk.

It is possible that the participant's urinary health outcomes may not improve during this research study or may even worsen. Potential physical side effects may exist when consuming dietary supplements. The potential risks of consuming the Flush Advanced+ product include:

<u>Side Effects and Risks</u>

10.2.20.1. Potential physical side effects of D-mannose include mild gastrointestinal discomfort, bloating, and loose stool.

10.2.20.2. Potential physical side effects of Vitamin C (as Calcium Ascorbate and Magnesium Ascorbate) include diarrhea, heartburn, nausea, upset stomach, and the development of kidney stones; these side effects are more common when taken at high doses.

10.2.20.3. Potential physical side effects of Vitamin B6 (as Pyridoxine HCl) include ataxia, nausea, headaches, photosensitivity, numbness, and reduced sensitivity to pain; these side effects are more common when taken at high doses.

10.2.20.4. Potential side effects of Magnesium (as Magnesium Ascorbate and Magnesium Citrate) include diarrhea, nausea, and vomiting; these side effects are more common when taken at higher doses.

10.2.20.5. Potential side effects of Potassium (as Potassium Citrate and Potassium Bicarbonate) include upset stomach, vomiting, and diarrhea. Additional potassium supplementation in patients with high potassium levels can cause cardiac issues, but hyperkalemic patients are excluded from participating in this study.

10.2.20.6. Potential side effects of cranberry include abdominal discomfort and diarrhea, though these side effects are rare and reported in supplementation at high doses.

To date, no serious adverse events have occurred for women who have used Flush Advanced+.

Interactions

- D-mannose has no known drug or supplement interactions, which may be due to lack of research.
- Cranberry has been shown to interact with the following medications:
    - Anisidine
    - Atorvastatin
    - Calcium channel blockers (e.g., nifedipine)
    - Warfarin
- Though unlikely at the dosage used in this study, Vitamin C (Calcium Ascorbate) has been shown to have several possible interactions with the following drugs and supplements:
    - Calcium channel blockers
    - Chemotherapy
    - Phosphate binders
    - Tetracycline antibiotics
    - Thiazide diuretics
    - Thyroid medications
    - Statins
    - Warfarin
- Vitamin B6 (as Pyridoxine HCl) has been shown to interact with the following medications:
    - Amiodarone
    - Barbiturates
    - Fosphenytoin and phenytoin
    - Levodopa
- Magnesium (as Magnesium Ascorbate and Magnesium Citrate) has been shown to interact with the following medications:
    - Sodium polystyrene sulfonate
    - Tetracycline antibiotics
- Potassium (as Potassium Citrate and Potassium Bicarbonate) has been shown to interact with the following medications:
    - ACE inhibitors
    - Angiotensin receptor blockers
    - Benadryl
    - Potassium-sparing diuretics

Although not all side effects and interactions are known, Flush Advanced+'s active ingredients are thought to be likely safe for most people who are eligible for this study when taken in moderate amounts and used as directed.

The research team will provide more information about the side effects, risks, and interactions upon request from the participant to ensure they feel safe to continue in the

study. The participant will be instructed to report any usual symptoms immediately to the research team.

10.2.21. Study Resources

Bonafide Health's Internal Participant Database includes approximately 20,000 women with varying urinogenital health symptoms who have communicated interest in participating in virtual studies. The research team will be able to recruit a portion of the 180-subject goal from the database. The research team will devote the necessary time to recruiting the specified number of participants in the agreed recruitment period.

All research team members have completed CITI Training for Human Research – Biomedical Research with Human Subjects. Furthermore, the research team is knowledgeable in conducting human research and has been educated on the study's research population.

The principal investigator – Dr. Trisha VanDusseldorp – has her PhD in Exercise Science with an emphasis in Nutritional Biochemistry and has been conducting human research for over 15 years. She will be responsible for all research team members ensuring they are adequately informed about the study protocol, the research procedures, and duties and functions.

The Medical Expert and Study Physician – Dr. Alyssa Dweck, MS, MD, FACOG is Bonafide's Chief Medical Officer and a practicing gynecologist. She is also an Assistant Adjunct Professor in the Department of Obstetrics, Gynecology at New York Medical College and a consultant at Massachusetts General Hospital, Vincent's Memorial Ob/Gyn Service. She has served on the board of directors of a large multi-specialty medical group in addition to ethics, quality assurance, and peer review committees.

Sub-Investigators on this trial have a combined, greater than 20 years of research experience and are well-equipped to handle this randomized controlled investigation.

10.3. Appendix 2: Questionnaires

10.3.1. Urinary Tract Infection Symptom and Impairment Questionnaire (UTI-SIQ-8)

How severe are your symptoms today? *

	Not at all	Mild	Moderate	Strong	Very strong
Urgency of urination	○	○	○	○	○
Pain or burning when passing urine	○	○	○	○	○
Frequency of urination	○	○	○	○	○
Pain in the lower abdomen	○	○	○	○	○

How impairing are your symptoms today? *

	Not at all	Mild	Moderate	Strong	Very strong
Impaired activities due to urgency	○	○	○	○	○
Impaired activities due to pain while passing urine	○	○	○	○	○
Impaired activities due to frequency of urination	○	○	○	○	○
Impaired activities due to pain in the lower abdomen	○	○	○	○	○

10.3.2. Recurrent Urinary Tract Infection Symptom Scale, Section C (RUTISS-C)

Recurrent Urinary Tract Infection Symptom Scale - Section C (RUTISS)

The following questions are about your UTI symptoms, and UTI-related pain or discomfort in your lower abdomen, genitals and/or bladder.

Please indicate whether you have experienced any of the following symptoms related to UTI in the PAST 24 HOURS, and, if so, how SEVERE they were: *

	Not present (0)	Very Mild (1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	Extremely severe (10)
Needing to urinate more frequently than normal.	○	○	○	○	○	○	○	○	○	○	○
Needing to urinate more urgently than normal.	○	○	○	○	○	○	○	○	○	○	○
Feeling as though you have the urge to urinate despite having just urinated.	○	○	○	○	○	○	○	○	○	○	○
Urine with an unusually strong or unpleasant smell.	○	○	○	○	○	○	○	○	○	○	○
Cloudy urine.	○	○	○	○	○	○	○	○	○	○	○
Debris or floating particles in your urine.	○	○	○	○	○	○	○	○	○	○	○
Pain or burning sensation when you are urinating.	○	○	○	○	○	○	○	○	○	○	○
Pain or burning sensation within the 30 minutes after urinating.	○	○	○	○	○	○	○	○	○	○	○
Pain or discomfort in your lower back.	○	○	○	○	○	○	○	○	○	○	○
Pain or discomfort in your side/flank.	○	○	○	○	○	○	○	○	○	○	○
Pain or discomfort radiating down into your legs.	○	○	○	○	○	○	○	○	○	○	○

10.3.3. Modified Recurrent Urinary Tract Infection Impact Questionnaire (m-RUTIIQ)

Recurrent Urinary Tract Infection Impact Questionnaire (RUTIIQ)

This questionnaire asks about the impact of your urinary tract symptoms on your personal wellbeing, social activities, work, and regular daily activities. It also asks about your feelings of satisfaction with your urinary tract symptom-related medical care.

Thinking about how you have felt in the past **TWO WEEKS**, please indicate how strongly you agree or disagree with the following statements.

Please consider the term "work" to include paid employment, volunteering, home management, caring responsibilities, and/or studying.

Because of my urinary tract health... *

	Strongly Disgree (0)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	Strongly Agree (10)
I have experienced feelings of anxiety.	○	○	○	○	○	○	○	○	○	○	○
I have experienced feelings of low mood or depression.	○	○	○	○	○	○	○	○	○	○	○
I have felt hopeless about the future.	○	○	○	○	○	○	○	○	○	○	○
I have avoided socializing more than I used to.	○	○	○	○	○	○	○	○	○	○	○
I have felt embarrassed in social situations.	○	○	○	○	○	○	○	○	○	○	○
I have felt that I am no longer close to anyone.	○	○	○	○	○	○	○	○	○	○	○
I have felt anxious in social situations.	○	○	○	○	○	○	○	○	○	○	○
I regularly miss full or partial days of work, home responsibilities, or studying.	○	○	○	○	○	○	○	○	○	○	○
The kind or amount of work I could do was limited.	○	○	○	○	○	○	○	○	○	○	○
It was more difficult than usual to concentrate on my work.	○	○	○	○	○	○	○	○	○	○	○
It was more difficult than usual to handle my workload.	○	○	○	○	○	○	○	○	○	○	○

Thinking about my urinary tract health-related medical care... *

	Strongly Disagree (0)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	Strongly Agree (10)
I have felt confident about being able to get the medical care I need.	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
I have felt like my medical concerns are taken seriously.	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
I have felt I could access UTI testing and treatment quickly enough.	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
I have had easy access to the medical specialists I need.	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯

The following questions are about the sexual impact of your urinary tract symptoms.

Do you feel your urinary tract symptoms have impacted your sex life in the past two weeks? *

- ◯ Yes
- ◯ No
- ◯ N/A, I was not sexually active in the past two weeks.

Thinking about how you felt in the past TWO WEEKS, please indicate how strongly you agree or disagree with the following statements. *

	Strongly Disagree (0)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	Strongly Agree (10)
I have avoided sexual activity to minimize risk of developing or worsening UTI symptoms.	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
I have felt unable to enjoy sexual activity due to my UTI symptoms.	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
I have been concerned about the impact of my UTI symptoms on my sex life and/or sexual relationship(s).	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯

10.3.4. Good vs. Bad Urinary Health Days – Daily Diary

How do you feel about your urinary health today? *



Good Bad

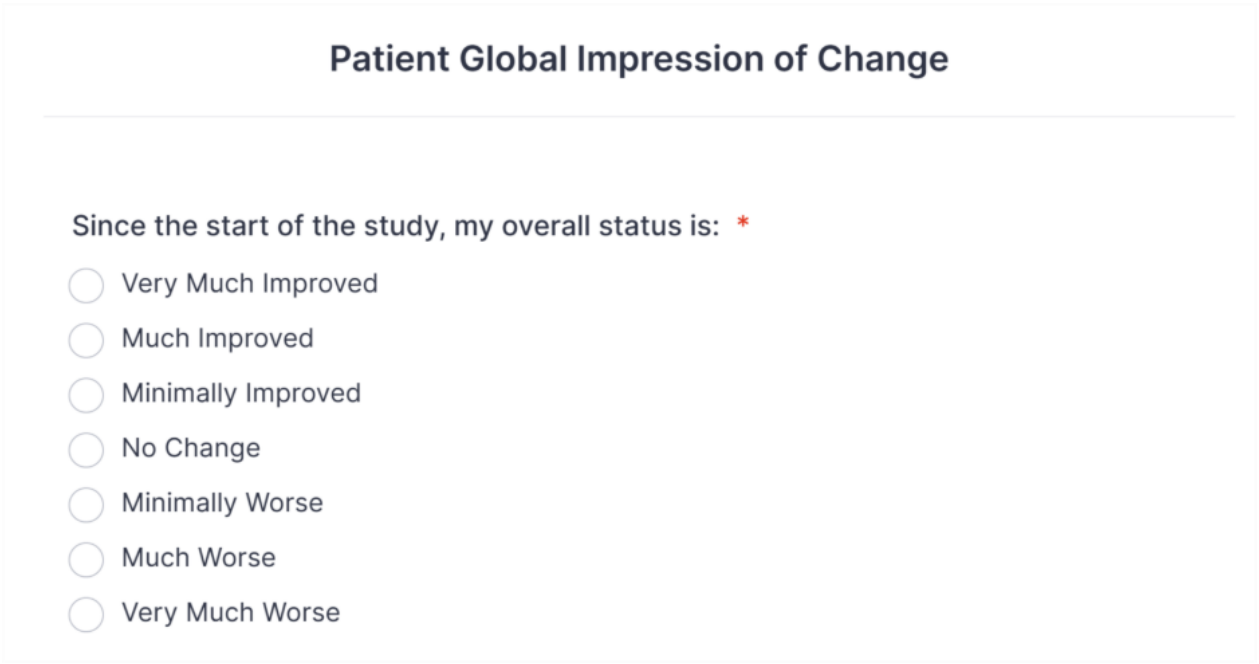
10.3.5. Patient Global Impression of Severity (PGIS)

Patient Global Impression of Severity

Please rate the severity of your urinary tract symptoms right now. *

- ○ Not Present
- ○ Very Mild
- ○ Mild
- ○ Moderate
- ○ Moderately Severe
- ○ Severe
- ○ Extremely Severe

10.3.6. Patient Global Impression of Change (PGIC)



Patient Global Impression of Change

Since the start of the study, my overall status is: *

- ○ Very Much Improved
- ○ Much Improved
- ○ Minimally Improved
- ○ No Change
- ○ Minimally Worse
- ○ Much Worse
- ○ Very Much Worse

10.3.7. Product Experience Questionnaire (PEQ)

Since starting this product... *

	Strongly Agree	Agree	Disagree	Strongly Disagree
I am less worried about my urinary health	○	○	○	○
I feel less worried about getting a UTI	○	○	○	○
I spent less time managing UTIs	○	○	○	○
I feel free to enjoy life without worrying about my urinary tract health	○	○	○	○
I feel more protected	○	○	○	○
I feel more confident	○	○	○	○
I feel more empowered	○	○	○	○
I feel more relieved	○	○	○	○
I notice an improvement in my urinary tract health	○	○	○	○
I felt less of a need for over-the-counter UTI pain medications	○	○	○	○
This product provides me an enjoyable way to take care of my urinary tract health	○	○	○	○
I would use this product over other over-the-counter products I've tried for UTI prevention	○	○	○	○

Thinking about my experience using this product... *

	Strongly Agree	Agree	Disagree	Strongly Disagree
I would use this product over other over-the-counter products I've tried for UTI prevention	○	○	○	○
I enjoy the taste of this product	○	○	○	○

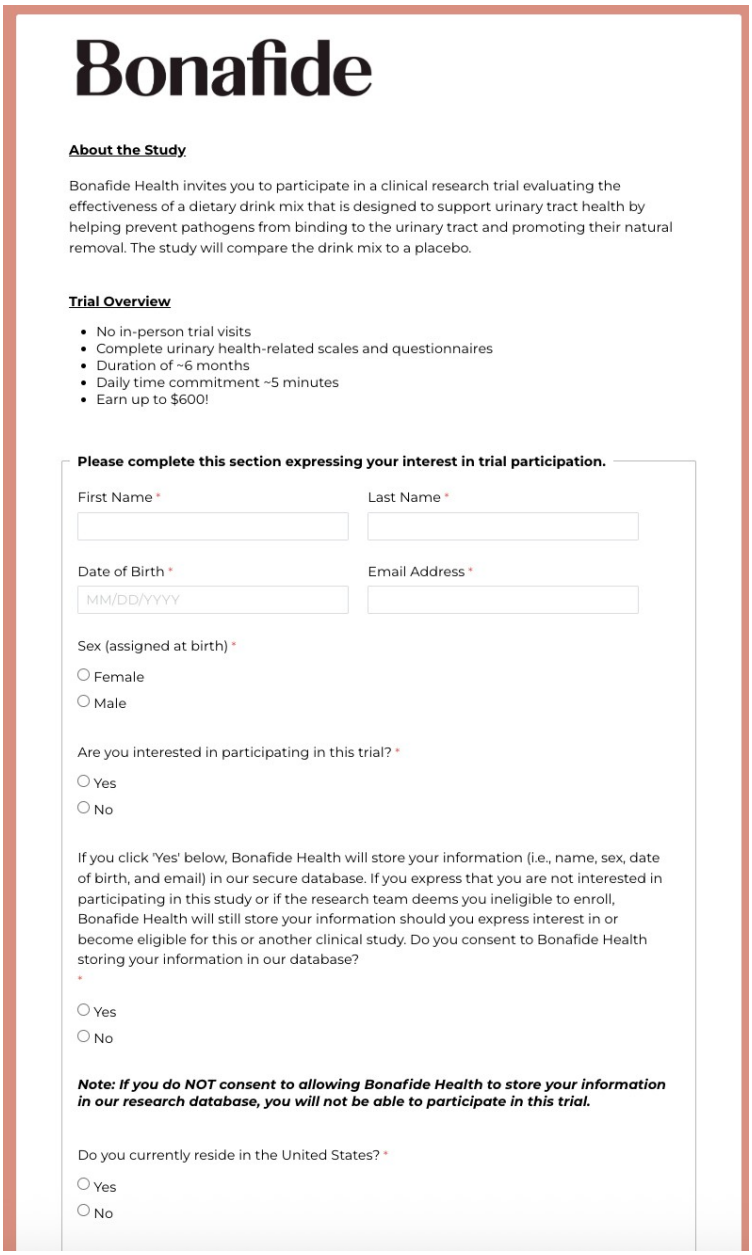
Are you sexually active? *

- ○ Yes
- ○ No

Since starting this product... *

	Strongly Agree	Agree	Disagree	Strongly Disagree
I feel less worried about getting a UTI after sex	○	○	○	○
I feel less anxious about having sex	○	○	○	○
I feel more comfortable having sex	○	○	○	○
I feel more confident being intimate	○	○	○	○
I worry less about how my UTI symptoms impact my sexual relationships	○	○	○	○
I feel more confident during vulnerable moments	○	○	○	○

10.3.8. Prescreener Questionnaire



Bonafide

About the Study

Bonafide Health invites you to participate in a clinical research trial evaluating the effectiveness of a dietary drink mix that is designed to support urinary tract health by helping prevent pathogens from binding to the urinary tract and promoting their natural removal. The study will compare the drink mix to a placebo.

Trial Overview

- No in-person trial visits
- Complete urinary health-related scales and questionnaires
- Duration of ~6 months
- Daily time commitment ~5 minutes
- Earn up to $600!

Please complete this section expressing your interest in trial participation.

First Name *

Last Name *

Date of Birth *

MM/DD/YYYY

Email Address *

Sex (assigned at birth) *

○ Female

○ Male

Are you interested in participating in this trial? *

○ Yes

○ No

If you click 'Yes' below, Bonafide Health will store your information (i.e., name, sex, date of birth, and email) in our secure database. If you express that you are not interested in participating in this study or if the research team deems you ineligible to enroll, Bonafide Health will still store your information should you express interest in or become eligible for this or another clinical study. Do you consent to Bonafide Health storing your information in our database?
*

○ Yes

○ No

Note: If you do NOT consent to allowing Bonafide Health to store your information in our research database, you will not be able to participate in this trial.

Do you currently reside in the United States? *

○ Yes

○ No

How did you hear about this trial? *

- ○ I received a text or email from the Bonafide Health or Uqora research team.
- ○ I learned about it from Live UTI Free.
- ○ I learned about it from my healthcare provider or clinic.
- ○ I received communication from Clinical Connection.
- ○ I received communication from L&E.

Conditional

Please tell us the name of the healthcare professional (i.e., doctor or PA) or clinic that informed you about this study. *

Conditional

The following questions will ask you about your Urinary Tract Infection (UTI) history.

1. Have you ever experienced a UTI? *

- ○ Yes
- ○ No

Conditional

2. Do you currently have an active UTI? *

- ○ Yes
- ○ No

Conditional

3. Please recall the date you began experiencing symptoms for your current UTI episode. *

MM/DD/YYYY

Conditional

3a. Please recall the **onset** date of your **most recent UTI**. *

MM/DD/YYYY

Conditional

3b. Please recall the **end** date (i.e., when your symptoms resolved) of your **most recent UTI**. *

MM/DD/YYYY

Conditional

4a. In the past **6 months**, how many UTIs have you experienced? Please only include UTIs that were accompanied by symptoms (i.e., urinary urgency, urinary frequency, painful urination, abdomen pain). *

Conditional

4b. How many of the UTIs you experienced in the last 6 months have been confirmed by a **urine culture test**? *

Conditional

5a. In the past **12 months** how many UTIs have you experienced? Please only include UTIs that were accompanied by symptoms(i.e., urinary urgency, urinary frequency, painful urination, abdomen pain). *

Conditional

5b. How many of the UTIs you experienced in the last 12 months have been confirmed by a **urine culture test**? *

Numb



10.4. Appendix 3: Supporting Documents

10.4.1. Advertisement

uti

uqora

Bonafide

Participants Needed for a Virtual Research Study on Bothersome Urinary Tract Symptoms

Scan Here to Apply

You May Be Eligible If You…

- Are a woman aged 18-75.
- Experience recurrent bothersome urinary tract symptoms and are otherwise healthy.
- Are willing and able to agree to the requirements of the study.

Trial Overview:

- All study tasks are completed virtually.
- You will receive a dietary supplement drink mix or identical placebo.
- You will track urinary health measures over the course of 6 months.
- There is a daily time commitment of ~5 minutes.
- You may earn up to $600 for your participation.

10.4.2. Screening and Enrollment Log

Screen ID	Name	Email	Date of Birth	Phone Number	Participant ID (for enrolled participants only)	Date of Consent	Version of Consent	Recruitment Route	Date Screened	Screening Status	Other, Specify	Ineligibilty Reason	Other, Specify2	Date Enrolled	Menopausa Status
1					BH-FADV-001										
2					BH-FADV-002										
3					BH-FADV-003										
4					BH-FADV-004										
5					BH-FADV-005										
6					BH-FADV-006										
7					BH-FADV-007										
8					BH-FADV-008										
9					BH-FADV-009										
10					BH-FADV-010										
11					BH-FADV-011										
12					BH-FADV-012										
13					BH-FADV-013										
14					BH-FADV-014										
15					BH-FADV-015										
16					BH-FADV-016										
17					BH-FADV-017										
18					BH-FADV-018										
19					BH-FADV-019										
20					BH-FADV-020										
21					BH-FADV-021										
22					BH-FADV-022										
23					BH-FADV-023										
24					BH-FADV-024										
25					BH-FADV-025										
26					BH-FADV-026										
27					BH-FADV-027										
28					BH-FADV-028										
29					BH-FADV-029										
30					BH-FADV-030										
31					BH-FADV-031										
32					BH-FADV-032										
33					BH-FADV-033										
34					BH-FADV-034										
35					BH-FADV-035										
36					BH-FADV-036										
37					BH-FADV-037										
38					BH-FADV-038										

10.5. Appendix 4: Abbreviations

Abbreviation	Definition
ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
ARB	Angiotensin II Receptor Blockers
BPS	Bladder Pain Syndrome
CFU	Colony Forming Unit
eICF	Electronic Informed Consent Form
EOS	End of Study
FAS	Full Analysis Set
GCP	Good Clinical Practice
HCP	Healthcare Provider
IC	Interstitial Cystitis

ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
MHQ	Medical History Questionnaire
N/A	Not Applicable
OAB	Overactive Bladder
PAC	Proanthocyanidin
PCOS	Polycystic Ovary Syndrome
PD	Protocol Deviation
PEQ	Product Experience Questionnaire
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PPS	Per Protocol Set
QOL	Quality of Life
M-RUTIIQ	Modified Recurrent Urinary Tract Infection Impairment Questionnaire
RUTISS-C	Recurrent Urinary Tract Infection Symptom Scale, Section C
SAE	Serious Adverse Event
SAF	Safety Set
SoA	Schedule of Activities
SOC	Standard of Care
SP	Study Product
UTI	Urinary Tract Infection
UTI-SIQ-8	Urinary Tract Infection Symptom and Impairment Questionnaire
WHO	World Health Organization

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