BIOMENDICS

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CLINICIAN REFERRAL PACKET

TAMES-02 Clinical Trial: Evaluating TolaSure in Epidermolysis Bullosa Simplex (EBS)

Study Sites:

Site Location	Site Principal Investigator	Site Contact Information
Stanford University School of Medicine, Department of Dermatology	Dr. Joyce Teng, PhD, MD jteng3@stanford.edu	Thomas Buschbacher tbusch@stanford.edu 650-313-0354
Northwestern University, Feinberg School of Medicine, Department of Dermatology	Dr. Amy Paller, MS, MD apaller@northwestern.edu	Lydia Rabbaa Khabbaz, BSND, PharmD, PhD lydia.rabbaakhabbaz@northwestern.edu 312-227-6817

Prepared for referring clinicians and healthcare partners

Dear Doctor,

We invite your collaboration in **TAMES-02**, a Phase II clinical study evaluating TolaSure, an investigational therapy in development for epidermolysis bullosa simplex (EBS). Your referrals are essential to fully evaluate this promising therapy. **We are also identifying additional clinical sites for a forthcoming Phase 3 program; please contact me directly if site participation is of interest.**

As you may know, Tolasure is an mTOR inhibitor intended to up-regulate autophagy, thereby removing mutant and aggregated keratin protein (e.g., KRT5/KRT14) within basal keratinocytes. By promoting **autophagy-mediated clearance of these aggregates,** TolaSure aims to improve cytoskeletal integrity, reduce epithelial fragility, and decrease the frequency and severity of blister initiation under mechanical stress.

In contrast to e.g., diacerein an IL-1β inhibitor that combats injury induced inflammation, TolaSure is being developed to intervene upstream at the level of keratinocyte resilience—with any reduction in inflammatory sequelae expected to be secondary to fewer/less severe blistering events.

Who to refer (high-level clinical hallmarks):

- **EBS, intermediate (generalized intermediate):** non-herpetiform blistering beyond acral sites; broader body-surface involvement; nail dystrophy common.
- **EBS, severe / Dowling–Meara (generalized severe):** marked fragility with herpetiform clustered blisters; widespread involvement

Referral notes and logistics:

- Please indicate if the patient is exiting another investigational study within the next 6 months; **TAMES-02 requires a ≥30-day washout** before initiating study medication.
- **Please complete and submit the referral form at the end of this document.**

Thank you for your partnership in bringing potential solutions to patients living with EBS.

Sincerely,
Karen McGuire, PhD, CEO
BioMendics, LLC
kmcguire@biomendics.com
ph#330-651-2140

I. Study Overview

- **Condition:** Epidermolysis Bullosa Simplex (EBS) – a rare, painful blistering skin disorder with no FDA-approved disease-modifying therapies.
- **Included Subtypes:** Intermediate or Severe EBS. Localized patients will be considered on a case-by-case basis if blistering occurs on non-palmoplantar surfaces (e.g. tops of the feet and hands, shins or arms) sufficient to meet BSA affected requirements.
    - **Intermediate EBS: Intermediate (Köbner/generalized intermediate, non-herpetiform):** Generalized blistering beginning at birth/early infancy with involvement beyond acral sites (trunk and extremities common), typically exacerbated by heat, friction, or minor trauma. Blistering is non-herpetiform and usually heals without atrophic scarring; dyspigmentation and milia can occur. Body-surface involvement is variable and waxes/wanes but is broader than acral-limited disease; mucosal disease is occasional, and nail dystrophy may be present. This phenotype sits between localized and severe EBS in overall blister burden.
    - **Severe EBS**: **Severe (Dowling–Meara / generalized severe):** Onset at birth with marked skin fragility and herpetiform (grouped/arciform) clusters of large blisters that may appear with minimal trauma or spontaneously; involvement is widespread across face, trunk, limbs, and acral sites, with flares producing extensive denuded areas. Oral mucosa is often affected; nail dystrophy and confluent palmoplantar keratoderma are common. Overall body-surface involvement is typically extensive and diffuse in early life, exceeding that of intermediate EBS.
- **Objective:** To evaluate the efficacy and safety of **TolaSure topical gel** in reducing blistering and improving patient outcomes.
- **Design:** Randomized, double-blind, placebo-controlled trial with open-label extension.
- **Duration:** ~6 months per participant (2 months double-blind, 2 months open-label, 2 months follow-up).
- **Sites:** Multi-center trial across leading academic medical centers.

II. Patient Eligibility (Quick Checklist)

Inclusion Highlights:
☐ Age **≥ 4 years**
☐ Confirmed or suspected epidermolysis bullosa simplex **intermediate (previously Köbner) to severe (previously EBS-Dowling Meara)** diagnosis (clinical and/or genetic confirmation)
☐ Willingness to participate in study visits and remote clinical imaging and PROs
Exclusion Highlights:
☐ Other forms of EB (e.g., dystrophic, junctional)
☐ Concurrent participation in another interventional trial

👉 *For referral criteria, please refer to the attached eligibility sheet-*CAN MY PATIENT QUALIFY?

III. Patient Participation

- **Eligibility:** Male or female ages 4 and up, diagnosed with intermediate to severe EBS
- **Visits:** ~3 in-person visits; remainder (~8 visits) via **remote / telehealth**
- **Support:** Travel, lodging, meals, and genetic testing (if needed) **fully covered**
- **Intervention:** Application of investigational topical gel to affected skin for 4-months, **patients have the option to treat their feet.**
- **Responsibilities:** Daily apply study gel, image treatment areas 1-2 times per week, fill-out weekly pain and itch questionnaires in diary, attend on-site and remote visits.
- **Monitoring:** Clinical chemistry labs (safety), adverse events (both serious and potential treatment-emergent AEs, safety), blister area measurements (efficacy), patient-reported outcomes (efficacy)

IV. Safety & Oversight

- Approved by Institutional Review Boards (IRBs) at each site
- Conducted under FDA IND with full compliance to **ICH-GCP standards**
- Ongoing oversight by independent Clinical Monitor
- Investigators brochure provided upon request

V. Referral Process

1. **Complete the referral form** (attached).
2. **Send securely** via fax or email
3. Study coordinator or investigator will respond and confirm eligibility and schedule screening.

TAMES-02 Clinical Trial Patient Referral Form Attached

VI. Patient Resources

Please share these materials with potential patients regarding the clinical trial:

- **Patient Ad:** Plain-language overview of TAMES-02
- **Support Resources:** Information on DEBRA, EB patient advocacy groups, and BioMendics website.

VII. Site Contacts

Site Location	Site Principal Investigator	Site Contact Information
Stanford University School of Medicine, Department of Dermatology	Dr. Joyce Teng, PhD, MD jteng3@stanford.edu	Thomas Buschbacher tbusch@stanford.edu 650-313-0354
Northwestern University, Feinberg School of Medicine, Department of Dermatology	Dr. Amy Paller, MS, MD apaller@northwestern.edu	Lydia Rabbaa Khabbaz, BSND, PharmD, PhD lydia.rabbaakhabbaz@northwestern.edu 312-227-6817

VIII. Appendices

- **APPENDIX 1:** TAMES-02 schematic diagram of the study design
- **APPENDIX 2**: Schedule of Events
- **APPENDIX 3:** Case example of an eligible patient

Link to ClinicalTrials.gov listing: NCT07027345

CAN MY PATIENT QUALIFY?

TAMES-02 REFFERRAL CRITERIA			
		YES	**NO**
1.	Is the patient at least 4 years of age?	☐	☐
2.	Does the patient have a diagnosis and clinical history of generalize intermediate (previously Köbner) to severe (previously EBS-DM) autosomal dominant EBS? **(Note: Please refer if patient has suspected EBS but lacks a formal diagnosis.)**	☐	☐
3.	A KRT5 or KRT14 autosomal dominant genetic mutation is required. **(Check yes if the specific mutation is unknown and genetic testing will be provided.)**	☐	☐
4.	Clinical history of EBS flares/blistering occur on anatomical areas other than the palms and soles (i.e., arms, legs, torso, tops of feet)? **(Note: Patient does not need to be actively flaring/blistering for referral.)**	☐	☐
5.	Is the patient currently enrolled in another interventional trial? **(If Yes: patient remains eligible; a 30-day washout may be required before dosing, depending on the prior study medication and route of administration.)**	☐	☐

TAMES-02 Clinical Trial Patient Referral Form

The BioMendics clinical trials team would like to thank you for your referral.

1. REFERRER CLINICIAN DETAILS

Name: _____

Title/Role: _____

Institution/Clinic Name: _____

Contact Number: _____

Email Address: _____

Secure Fax: _____

Signature: _____ Date: _____

2. PATIENT INFORMATION (DE-IDENTIFIED IF EXTERNAL)

Initials: _____ Date of Birth (or Age): _____

Sex: ☐ Male, ☐ Female, ☐ Other EB Simplex Diagnosis: _____

Date of Diagnosis (if known): _____

EB Simplex Gene Mutation: _____, or ☐ Needs Genetic Testing

3. RELEVANT MEDICAL / TREATMENT HISTOY

Current Medications:

_____

_____

Previous Treatment for EBS:

_____

Has the patient participated in another investigational trial in the last 6 months?

☐ YES-Provide date of exit: _____

Confirm washout period of ≥30 days before TAMES-02 enrollment:

☐ Confirmed, ☐ Not Confirmed

☐ NO, patient has not participated in another investigational trial in the last 6 months

RELEVANT MEDICAL / TREATMENT HISTOY (CONTINUED)

Notable comorbidities: _____

Any contraindications you are aware of: _____

_____

4. REFERRAL DETAILS

Date of referral: _____

Has patient expressed interest in trial participation? ☐ Yes, ☐ No, ☐ Unsure

Comments/Notes: _____

_____

5. SUBMISSION INSTRUCTIONS

Email the completed form to the Principal Investigator (PI) and study contact at your nearest participating site.

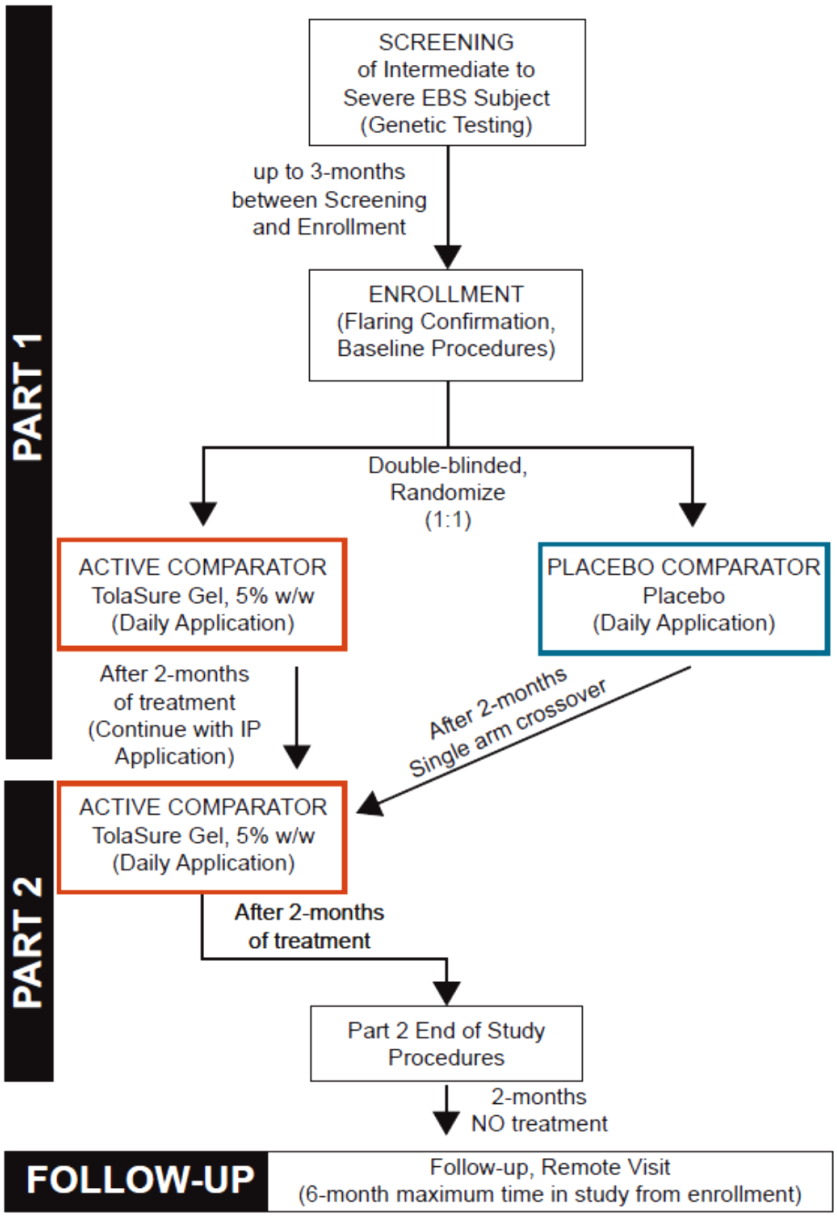
Site Location	Site Principal Investigator	Site Contact Information
Stanford University School of Medicine, Department of Dermatology	Dr. Joyce Teng, PhD, MD jteng3@stanford.edu	Thomas Buschbacher tbusch@stanford.edu
Northwestern University, Feinberg School of Medicine, Department of Dermatology	Dr. Amy Paller, MS, MD apaller@northwestern.edu	Lydia Rabbaa Khabbaz, BSND, PharmD, PhD lydia.rabbaakhabbaz@northwestern.edu

Stite contact or investigator will contact your office to confirm receipt, PTC/HIPAA, and arrange follow-up with the patient to conduct screening and confirm eligibility.

⚠ **Privacy Note:** This form is intended for research referral purposes only. Please do not include full identifiers (full name, SSN, insurance details) unless the referral is within the same covered health system and HIPAA permits.

APPENDIX 1

TAMES-02 Phase II Study Design, Randomized, Double-Blinded, Single Arm Crossover with Follow-up



This illustration shows the overall study design and timeline for the TAMES-02 Phase II clinical trial in adults and children with generalized intermediate to severe EBS. This is a randomized, double-blinded study with a single arm crossover, after 2-months of daily application of either the TolaSure Gel, 5% w/w or Placebo to target lesional areas (TLAs). After the crossover all subjects will continue daily application of TolaSure Gel, 5% w/w for an additional 2 months. There will be a 2-month follow-up visit after Part 2 and end of study (EOS) procedures.

APPENDIX 2

TAMES-02 Schedule Highlights:

- **Three (3) on-site visits**: Baseline, Part 1 End of Study (at 2 months), Part 2 End of Study (at 4 months)
- **Eight (8) bi-weekly remote visits**. Final remote visit is a Follow-up Visit after~ 6-months study participation.
- **Genetic testing provided** during screening, if needed
- Clinical chemistries, urinalysis, and urine pregnancy testing at baseline and at 4-month (Part 2 End of Study)
- **Investigational Product Application Schedule:**
    - Part 1 of Study-Daily topical application for 2 months. Patients are blinded to treatment and will receive either TolaSure Gel or Placebo Gel
    - Part 2 of Study-Daily topical application for an additional 2 months. **All patients will receive TolaSure Gel.**
- **Patients can treat their feet** as part as a secondary outcome.
- **Patient Responsibilities:**
    - Patients will record IP applications in their Patient Diary
    - Patients will take images (1-2 times per week) of their treatment areas using a dedicated iPhone.
    - Patients will fill out weekly questionnaires on pain and itch in their diary.

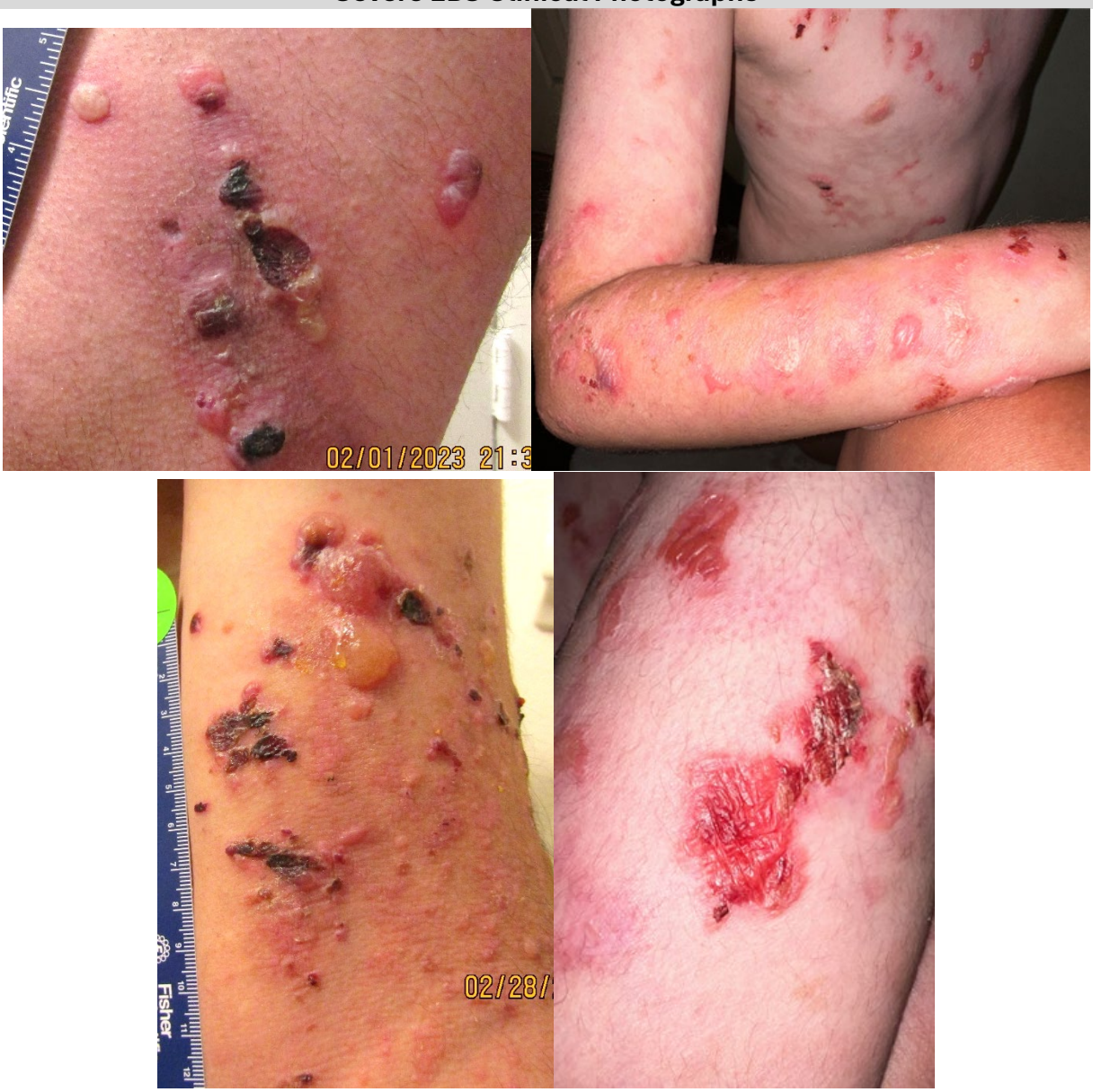
APPENDIX 3

Example of an Eligible Patient for the TAMES-02 Study

Eligibility Overview

- Subject Male
- 13 years old
- KRT 5/ KRT 14 Gene Mutation, confirmed.
- Clinical Presentation-Blistering and flaring occurs on lower legs and is 2-3% body surface area (BSA)
- Parent consent and child assent on file

Severe EBS Clinical Photographs



Example of Eligible Patient for the TAMES-02 Study (Continued)

Intermediate EBS Clinical Photographs