EPP L.I.G.H.T. (Life Impact and Genetic Health Trajectory) (E.U.) Study: A CROSS-SECTIONAL ONLINE SURVEY OF ADULT AND ADOLESCENT PARTICIPANTS WITH ERYTHROPOIETIC PROTOPORPHYRIA (EPP) OR X-LINKED PROTOPORPHYRIA (XLP)

Study sponsor:
Disc Medicine
321 Arsenal Street, Suite 101
Watertown, MA 02472
USA

Study conducted by:
Sciensus International B.V
Bijsterhuizen 3142
6604 Lv Wijchen
Netherlands

Responsible for implementing and overseeing the study:
Mathieu Loiseau, Director of Rare Clinical Operations, Sciensus
mathieu.loiseau@sciensus.com

PROTOCOL SYNOPSIS

Title	**EPP L.I.G.H.T. (Life Impact and Genetic Health Trajectory) (E.U.) Study: A CROSS-SECTIONAL ONLINE SURVEY OF ADULT AND ADOLESCENT PARTICIPANTS WITH ERYTHROPOIETIC PROTOPORPHYRIA (EPP) OR X-LINKED PROTOPORPHYRIA (XLP)**
Objective	To describe the burden associated with erythropoietic (EPP) protoporphyria and X-linked protoporphyria (XLP) in terms of health-related quality of life (HRQoL), symptoms, healthcare resource utilization (HCU), and preferences for treatment. .

Study Design	This is a cross-sectional, online survey study. Individuals with EPP/XLP will complete a one-time online questionnaire. The questionnaire includes existing, validated and original patient-reported outcome (PRO) measures to assess HRQoL including the EPP Impact Questionnaire (EPIQ) (not yet validated), items assessing early warning symptoms and pain from EPP (Sunlight Exposure Diary) (not yet validated), selected domains from the KIDSCREEN-27 [Psychological Well-Being, Peers and Social Support, and School Environment] (adolescents only), PROMIS Satisfaction with Social Roles and Activities – 8a (adults and adolescents), PROMIS Peer Relationships - 8a (adolescents only), PROMIS Social Isolation - 4a (adults and adolescents), and original items assessing physical functioning, anxiety, depression, fatigue, bullying/treated unfairly, work/school loss/productivity, and need for accommodations in doing daily activities. In addition, original items are included to assess the diagnosis of EPP/XLP and HCU, such as hospitalizations, emergency room visits, physician visits, and prescription and over-the-counter medications. The survey also includes questions assessing the preference for various types of EPP/XLP treatment. Demographic and clinical information will also be collected to describe the study population. Individuals ≥12 years old with EPP/XLP in the UK, France, Germany, Italy, and Spain will be recruited via patient advocacy groups (PAG), including, but not limited to Selbsthilfe EPP e.V. (Germany), Association Française des Malades Atteints de Porphyrie (France), PORFIR.I.A Domenico Tiso - Associazione Italiana malati di porfiria Domenico Tiso (Italy), The British Porphyria Association (UK) and Asociación Española de Porfiria (Spain).

Sample Size	Approximately 100 individuals with EPP/XLP will be enrolled and will complete the questionnaire. Ideally, up to 25 adolescents will be recruited of the total sample of participants. The goal will be to recruit a heterogenous, diverse population with EPP/XLP. A power calculation was not conducted given the descriptive nature of the prespecified analyses. A sample of 100 was identified as feasible given the rarity of EPP/XLP, with an estimated prevalence of 1 in 200,000 to 1 in 57,000.

Summary of Eligibility Criteria	Inclusion Criteria 1. ≥12 years of age 2. Have a diagnosis of EPP/XLP 3. Reside in the UK, France, Germany, Spain, or Italy 4. Able to speak, read, and write English, French, German, Spanish, Italian or Welsh. ~~5. Able to provide consent to participate~~ ~~6.~~5. Willing to complete one online questionnaire that will take approximately 60 minutes to complete Exclusion Criteria Presence of a medical or psychiatric condition or treatment for condition that results in a cognitive or other (e.g., visual, ~~hearing)~~ impairment that would interfere with participating in the study.
Procedures	**Study Advertising** The Study Advert (Appendix A) will be disseminated by Patient Advocacy Groups (PAG) within the countries in scope. Dissemination methods may include PAG's website, social medias or newsletters. **Participant Information** Individuals interested in taking part will be required to download and read the relevant Participant Information Sheets (Appendix F, G and H) via the link indicated on the Study Advert. When the participant is an adolescent aged between 12 and 15, parents/caregivers will be invited to read the adolescent participant information sheet with them. **Participants' registration onto the Study** Interested individuals aged 12 or above will be invited to register via a QR code or weblink provided on the participant information sheet. When the participant is a child and does not have an email address, their parents or caregivers can register them, provided the child is willing to take part. **Eligibility Screening** Clinical study nurses employed by Sciensus in each participating country will be responsible for screening the potential participants who have self-registered. They will schedule screening phone calls to verify that participants meet the eligibility criteria for the study (Appendix B). The nurse must obtain permission to speak to participants aged 12-15 from a parent/caregiver/legal representative prior to screening

	Once eligibility is confirmed, a unique survey link will be sent to each participant via email. During the screening calls, potential participants will be able to ask the clinical study nurses any questions they may have about the study. **Consent:** Consent for taking part in an online survey is normally implied by the completion of the questionnaire by participants. However, participants in the EPP L.I.G.H.T (E.U) Study will be asked to agree electronically with a series of statements related to consent and the use of personal data. When the participant is aged between 12 and 15 years, this consent form must be completed by a parent, caregiver, or other legal representative. (Appendix C). **Questionnaire completion:** Adults and adolescents with EPP/XLP will complete a one-time, online questionnaire about their experience with EPP/XLP. The questionnaire will be hosted on an Electronic Data Capture platform provided by Climedo™ and managed by Sciensus. The survey will be available in English, French, German, Italian, Spanish, and Welsh and participants will be able to choose their preferred language no matter where they are located. The questionnaires are intended to be completed independently by participants, irrespective of age. However, in the case of adolescent participants, a parent, caregiver, or other legal representative may provide assistance with understanding the questions and completing the survey. **Voucher:** Each participant will be compensated with a voucher after completing the questionnaire.

Analysis	Raw anonymized data will be analyzed by a US-based company called Health Outcome Solutions. Quantitative data will be analyzed by a descriptive manner following the statistical analysis plan (SAP). An aggregate, high-level summary in layman's terms will be shared with the Patient Advocacy Groups. This high-level summary will be available in English, French, German, Italian, Spanish, Welsh and

	Catalan.
Sponsor	Disc Medicine, Inc.

EPP L.I.G.H.T. (Life Impact and Genetic Health Trajectory) Study: A CROSS-SECTIONAL, ONLINE STUDY IN ADULT AND ADOLESCENT PARTICIPANTS WITH ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

INTRODUCTION

Erythropoietic Protoporphyria (EPP) is a rare, inherited metabolic disorder characterized by a deficiency of the enzyme ferrochelatase (FECH); less commonly it is caused by a gain of function mutation in the ALAS2 enzyme X- linked Protoporphyria (XLP) is clinically indistinguishable from EPP and caused by increased activity of the enzyme aminolevulinic acid synthase (ALAS2). The primary sign of EPP/XLP is hypersensitivity of the skin to sunlight and to some types of artificial light (e.g., fluorescent light). Symptoms after exposure to light include burning, itching and pain on exposed areas of the skin. Affected individuals may also experience edema and/or redness or inflammation of the skin. The hands, arms, and face are most commonly affected. EPP affects males and females similarly and is estimated to occur in about 1 in about 74,300 individuals. The onset of skin symptoms generally occurs in infancy; however, in some cases, onset may not occur until adolescence or adulthood.

This cross-sectional, online survey study will be used to describe the burden associated with EPP/XLP in terms of health-related quality of life (HRQoL), symptoms and healthcare resource utilization (HCU), and preference for treatment. The questionnaire includes several existing, validated and original patient-reported outcome (PRO) HRQoL measures including the EPP Impact Questionnaire (EPIQ) (not yet validated), items assessing early warning symptoms and pain from EPP (Sunlight Exposure Diary) (not yet validated), selected domains from the KIDSCREEN-27 [Psychological Well-Being, Peers and Social Support, and School Environment} (adolescents only), PROMIS Satisfaction with Social Roles and Activities – 8a (adults and adolescents), PROMIS Peer Relationships -8a (adolescents only), PROMIS Social Isolation 4a (adults and adolescents), and original items assessing physical functioning, anxiety, depression, fatigue, bullying/treated unfairly, work/school loss/productivity, and need for accommodations in doing daily activities. Original items assessing EPP/XLP diagnosis and HCU, such as visits to the emergency room or hospital, visit to physicians, and use of both prescription and over-the-counter medication use are also to be included. Newly developed items are also included to assess experience with and preference for various modes of treatment administration (e.g., oral vs. implant). Finally, participants will also complete questions assessing demographic and clinical characteristics to assist in describing the study population. The online questionnaire will be hosted and managed by Climedo™.

PURPOSE AND OBJECTIVE

This study is conducted in the interest of public and societal well-being. The purpose of this study is to explore and describe the lived experiences of individuals diagnosed with EPP/XLP in a context where research and understanding of this condition is limited.

The objective of this study is to:

- Describe the experience of individuals with EPP/XLP. Specifically, the questionnaire will contain questions to describe the following concepts:
  - Health-Related Quality of Life (HRQoL)
  - Healthcare resources Utilization (HCU)
  - Clinical and demographic characteristics
  - Patient preference for various modes of treatment
- The findings from the survey will be summarized in a final report, two abstracts, and a manuscript.

STUDY DESIGN/PROCEDURES

Participants will be identified with assistance from advocacy groups including but not limited to Selbsthilfe EPP e.V. (Germany), Association Française des Malades Atteints de Porphyrie (France), PORFIR.I.A Domenico Tiso - Associazione Italiana malati di porfiria Domenico Tiso (Italy), The British Porphyria Association (UK) and Asociación Española de Porfiria (Spain).

1- Study advertising

The Study Advert (Appendix A) will be disseminated by the relevant Patient Advocacy Groups (PAG) within the countries in scope. Dissemination methods may include PAG's website, social medias, newsletters etc…

2- Participant information

Individuals interested in taking part will be required to download and read the relevant Participant Information Sheets (Appendix F, G and H) via the link indicated on the Study Advert. When the participant is an adolescent aged between 12 and 15, parents/caregivers will be invited to read the adolescent participant information sheet with them.

In accordance with local laws and Regulation(EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data, the participants are informed about the objectives of the study, the nature of the collected data, the data recipients, the place and duration of data storage and about their rights.

3- Participant's registration onto the study

Interested individuals aged 12 or above will be invited to register via a QR code or weblink provided on the participant information sheet. When the participant is a child and does not have an email address, their parents or caregivers can register them, provided the child is willing to take part.

4- Eligibility screening by Clinical Study Nurses

Upon registration a Clinical study nurse~~s~~ employed by Sciensus will contact the participant via email to schedule a screening call. The nurse must obtain permission to speak to participants aged 12-15 from a parent/caregiver/legal representative prior to screening. During th~~is~~e screening phone call potential participants will need to be able to provide confirmation of their diagnosis (Appendix B). When eligibility is confirmed a unique link to the online questionnaire will be sent to the participant's email address.

During the screening calls, potential participants will be able to ask the clinical study nurses any questions they may have about the study.

5- Consent

Participants in the EPP L.I.G.H.T (E.U) Study (or a parent, caregiver or other legal representative for participants aged between 12 and 15) will be asked to agree electronically with a series of statement related to consent and the use of personal data (Appendix C).

6- Questionnaire completion

The online survey comprises questions about how EPP/XLP affects participants' daily life, including physical symptoms (such as early warning signs and pain), mental health, social relationships, and the need for accommodation at work or school. Some of the questions come from well-established questionnaires, while others were designed specifically for this study to address areas unique to EPP/XLP. For adolescents, the survey includes measures focused on psychological well-being, social support, and school environment. Adults and adolescents will answer questions about satisfaction with social roles, relationships, and feelings of isolation.

The survey also asks about participants' experience with healthcare, including visits to doctors or hospitals and the use of medications. Additionally, questions will explore preferences for different treatment methods and gather basic information about participants' demographic and clinical backgrounds to provide a clearer picture of the study population.

It is anticipated that the questionnaire will take around 60 minutes to complete. Participants will be able to do this at their own pace over several days by saving their responses and returning when convenient.

The questionnaires are intended to be completed independently by participants, irrespective of age. However, in the case of adolescent participants, a parent, caregiver, or other legal representative may provide assistance with understanding the questions and completing the survey.

PARTICIPANT ELIGIBILITY

To participate in this study, participants must meet the following eligibility criteria:

Inclusion Criteria

1. ≥12 years of age
2. Have a diagnosis of EPP/XLP
3. Reside in the UK, France, Germany, Italy, or Spain.
4. Able to speak, read, and write English, French, German, Italian, Spanish, or Welsh.
5. Willing to complete one on-line questionnaire that will take approximately 60 minutes to complete

Exclusion Criteria

Presence of a medical or psychiatric condition or treatment for condition that results in a cognitive or other (e.g., visual~~, hearing~~) impairment that would interfere with participating in the study (at the discretion of the investigator)

SAMPLE SIZE

A power calculation was not conducted given the descriptive nature of the prespecified analyses. Given the rarity of EPP/XLP, with an estimated prevalence of 1 in 200,000 to 1 in 57,000 a sample of 100 was identified as feasible to describe the burden associated with EPP/XLP (in terms of HRQoL, symptoms, HCU, and preferences for treatment). The goal is to ideally enroll ~ 75 adults and ~ 25 adolescents with EPP/XLP, but no quotas will be imposed. Enrollment may be augmented to achieve this target number of complete responses.

To the extent possible, an effort will be made to diversify recruitment based on demographic characteristics so that participants enrolled represent a heterogeneous sample across males and females of all ages, educational levels, race, geographic location, and time since diagnosis.

QUESTIONNAIRES

Copies of adolescent and adult questionnaires can be found in Appendix D and E. The questionnaire should take participants approximately 60 minutes to complete. The content of the Adult and Adolescent versions of the questionnaires are described below.

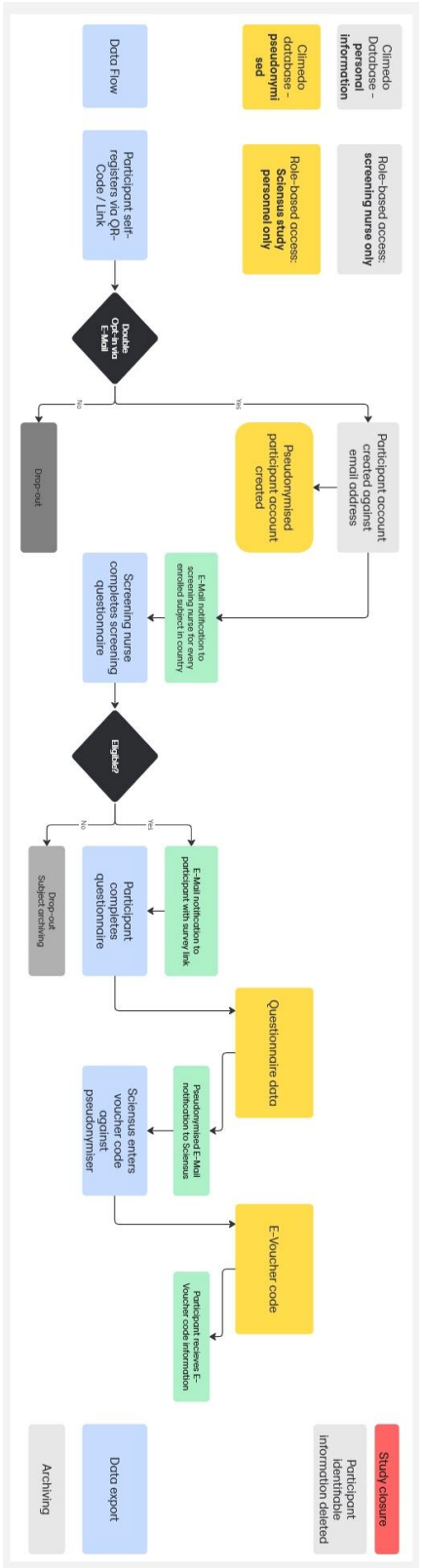
Adult and Adolescent Questionnaires

Table 1 includes all the concepts that are assessed, questionnaire number, and source.

Concept	Question Numbers – Adult Version	Question Numbers- Adolescent Version	Source
Diagnosis of EPP/XLP	1-6	1-5	Original
Frequency of physician visits	7-8	6-7	Original
Tracking of protoporphyrin levels	9	8	Original
Co-morbid conditions	10-13	9-10	Original
Early warning symptoms	14, 15	11, 12	Original
Severity of early warning symptoms	16	13	Sunlight Exposure Diary
Frequency of full reaction	17	14	Original
Frequency of early warning symptoms before full reaction	18	15	Original
Date of last full reaction	19	16	Original
Time in sunlight/time to resolve full reaction	20-22	17-19	EPIQ
Pain from full reaction	23	20	Sunlight Exposure Diary
Impact on daily activities due to pain from full reaction	24	21	Original
Physical functioning	25-27	22-24	Original
Psychological Well-Being	N/A	33-39	KIDSCREEN- 27
Peers and Social Support	N/A	40-43	KIDSCREEN- 27

Peer relationships	N/A	44-51	PROMIS Peer Relationships -8a
Social isolation	36-39	52-55	PROMIS Social Isolation 4a
Bullied	40	56	Original
Treated unfairly	41	57	Original
Emotions (depression/anxiety)	42-46	58-62	Original
Daily activities	47	63	EPIQ
Accommodations to do daily activities	48	64	Original
Activities without accommodations	49	65	Original
Daily activities	50	66	Original
Fatigue	51	67	Original
QoL	52-53	68-69	EPIQ
General health	54	70	KIDSCREEN- 27/SF-36
Work loss/productivity	55-57	71-73	Original
School loss/productivity	58-60	74-76	Original
Health care utilization	61-67	77-83	Original
Treatment satisfaction/preferences	68-73	84-89	Original
Special equipment/clothing	74	90	Original
Demographic questions	75-81	91-96	Original

DATA FLOW


Climedo Database – personal information
Climedo database-pseudonymised
Data Flow
Role-based access: screening nurse only
Role-based access: Sciensus study personnel only
Participant self-registers via QR-Code / Link
Double Opt-in via E-Mail
No
Yes
Drop-out
Pseudonymised participant account created
Participant account created against email address
E-Mail notification to screening nurse for every enrolled subject in country
Screening nurse completes screening questionnaire
Eligible?
No
Yes
Drop-out Subject archiving
Participant completes questionnaire
E-Mail notification to participant with survey link
Questionnaire data
Pseudonymised E-Mail notification to Sciensus
Sciensus enters voucher code against pseudonymiser
E-Voucher code
Participant recieves E-Voucher code information
Study closure
Participant identifiable information deleted
Data export
Archiving

COMPENSATION

Each participant will receive a £80 / €95 shopping voucher upon completion of the questionnaire which Sciensus will be responsible for administering and which will be available immediately to participants upon completion of the questionnaire.

ANALYSIS

Descriptive analyses will be performed for the total population, adolescents (12 to <18 years of age), and adults ≥ 18 years of age, separately. Separate tables will be prepared for data concepts being assessed. If sample size permits, sub-group analyses may be conducted among adults by age (e.g., 18 to 39 years and ≥40 years), sex, time since diagnosis, and satisfaction with current EPP/XLP treatment. In addition, sample size permitted, the statistical significance of differences between adults and adolescents and between disease characteristics and health-related quality of life will be estimated. All analyses will be conducted using SAS Version 9.4.

A detailed SAP (Appendix I) has been prepared. It includes table shells, with input from Disc and the project team, on the process that will be used to analyze and present the findings from the survey.

DISSEMINATION

The sponsor, Disc Medicine, Inc., will prepare a final report detailing the methods and findings from the cross-sectional, online study. The goal will be to also submit two abstracts to scientific meetings, and one manuscript to a peer-reviewed journal highlighting the key findings. Additionally, an aggregate high-level summary in layman's terms will be shared with Patient Advocacy Groups.

PROVISIONAL TIMELINE

Online survey Go-live: Q3 2025
Online survey Close: Q4 2025 (3 months after go-live)
Database lock and study close-off: Q4 (2 weeks after survey closes)
Data analysis and medical writing completed by 15th December 2025.

CONFIDENTIALITY OF DATA

Data will be processed in accordance with local laws and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data, all records and subject's identity will remain confidential.

The online study will be hosted onto the Climedo™ system. This system uses the data

center of AWS located in the Frankfurt (eu-central-1) region to host the data.

No personal identifiable other than the participant email address will be recorded.

A random unique participant number will be created, and the study-related data will be recorded against this number. The Climedo™ system uses an electronic data management system designed to ensure strict separation between personally identifiable information (PII) and study-related data. The two datasets are linked exclusively through a unique, encrypted key. This key is securely managed by the software provider's technical team and cannot be accessed by the study sponsor, investigators, or any other third party. Only authorised members of the software provider's technical team have the ability to link the two databases if required for system maintenance or data integrity verification purposes.

Only raw anonymised data will be provided to the data analyst.

Personal identifiable data (email) will be deleted within 90 days of study closure.

ETHICAL REVIEW AND REGULATORY CONSIDERATIONS (WHEN APPLICABLE)

Observational studies will be submitted to ethical review boards (ERBs) for approval or waivers sought whenever required by local law. Regulatory authorities will be notified, and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Pharmacoepidemiology Practices (GPPs) and applicable laws and regulations of the country or countries where the study is being conducted, as appropriate.

APPENDICES

Appendix A : Study advert
Appendix B : Screening questionnaire
Appendix C: eConsent statement
Appendix D: Questionnaire – Adult version
Appendix E: Questionnaire – Adolescent version
Appendix F: Information for Adolescent between 12 and 15
Appendix G: Information for Adults and Adolescent above 16
Appendix H: Information Sheet for Parents or Caregivers
Appendix I: Statistical Analysis Plan