

# Cohort Profile Update: The Swiss Eosinophilic Esophagitis Cohort Study (SEECs)

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## Keywords

Eosinophilic esophagitis · Cohort · Adults

## Abstract

**Introduction:** The Swiss Eosinophilic Esophagitis Cohort Study (SEECs) is a national cohort that was established in 2015 with the aim of improving quality of care of affected adults with eosinophilic esophagitis (EoE). Between 2020

and 2022, paper questionnaires were gradually replaced by fully electronic data capture using Research Electronic Data Capture (REDCap<sup>®</sup>) software. We aim to provide an update of the SEECs 8 years after its launch. **Methods:** The SEECs prospectively includes adults ( $\geq 18$  years of age) with EoE as well as patients with gastroesophageal reflux disease (GERD) and healthy control subjects (HC). Upon inclusion and follow-up (typically once every 12–18 months), patients and physicians complete REDCap<sup>®</sup> questionnaires, which are

available in German, French, and English. Patient-reported outcomes (PROs) and biologic findings are assessed on the same day using validated instruments (EeAI PRO for symptoms; EoE-QoL-A for QoL; EREFS for endoscopic activity; modified EoE-HSS for histologic activity). The SEECs biobank includes biosamples from patients with EoE, GERD, and HC. **Results:** As of July 2023, the SEECs included 778 patients (716 [92%] with EoE, 29 [3.8%] with GERD, and 33 [4.2%] HC; 559/778 [71.9%] were male). Mean age  $\pm$  SD (years) at enrollment according to diagnosis was as follows: EoE  $41.9 \pm 12.9$ , GERD  $53.6 \pm 16.4$ , HC  $51.7 \pm 17.2$ . Concomitant GERD was found in 200 patients (27.9%) of the EoE cohort. Concomitant allergic disorders (asthma, rhinoconjunctivitis, eczema) were present in 500 EoE patients (74.4%). At inclusion, 686 (95.8%) of EoE patients were on ongoing treatment (orodispersible budesonide tablet [Jorveza®] in 281 patients [41%]; budesonide or fluticasone syrup or swallowed powder in 290 patients [42.3%]; proton-pump inhibitors in 162 patients [23.6%]; elimination diets in 103 patients [15%]; and esophageal dilation at last visit in 166 patients [24.2%]). A total of 8,698 biosamples were collected, of which 1,395 (16%) were used in the framework of translational research projects. **Conclusion:** SEECs continuously grows and is operational using fully electronic data capture. SEECs offers up-to-date epidemiologic and real-world clinical efficacy data on EoE and promotes clinical and translational research.

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## Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory disease that was first described in the early 1990s in Switzerland by Straumann and in the USA by Attwood [1, 2]. Diagnosis is based on symptoms of esophageal dysfunction, a dense eosinophilic infiltration with at least 15 eosinophils per high-power field and the exclusion of other conditions associated with esophageal eosinophilia [3–5]. The prevalence of EoE ranges between 28.1 and 56.7/100,000 with incidence rates between 5 and 10/100,000, both higher for adults than for children and the elderly [6–8]. While the increase in prevalence is explained by EoE's chronic nature, the rapid increase in its incidence constitutes a true non-artifactual rise with a potential role for increased disease recognition and detection [9–12]. EoE is a food-allergen and, to a lesser degree, aero-allergen-driven disease. Untreated inflammation leads to esophageal stricture formation in the majority of patients [13]. EoE is commonly associated with allergic disorders, present in up to

60–80% of patients (allergic rhinitis, asthma, IgE-mediated food allergy, atopic dermatitis) [14, 15]. Major progress was made over the last three decades regarding the assessment of EoE activity on the level of patient-reported outcomes (PROs, encompass symptoms and quality of life) as well as endoscopic and histologic disease activity [16]. The different instruments to measure EoE activity, stratified according to different clinical frameworks, are summarized in Table 1. Esophageal distensibility plateau and secondary peristalsis can be assessed using the Functional Lumen Imaging Probe (FLIP™) [17]. Given the chronic nature of EoE with the inherent risk of stricture development in the long term, the vast majority of patients will need treatment [7, 13]. Treatment options include drugs (swallowed topical steroids [Jorveza®, swallowed budesonide or fluticasone either in the form of a slurry syrup or swallowed as powder], proton-pump inhibitors [PPIs], dupilumab [Dupixent®]), elimination diets, and esophageal dilation [18]. Despite the major progress that has been made over the last three decades, multiple questions remain open that are best addressed using a cohort study. Some of these are noted:

1. Do all EoE patients need maintenance therapy?
2. Are there clinical predictors to identify a more aggressive phenotype that is prone to stricture formation and food bolus impactions?
3. What is the effectiveness of swallowed topical steroids, PPIs and dupilumab in daily practice?
4. Is the use of swallowed topical steroids associated with an increased risk of osteoporosis and adrenal axis suppression?

## Methods

### *Swiss EoE Cohort Study from 2015 to 2023: A Historical Overview*

The Swiss Eosinophilic Esophagitis Cohort Study (SEECs) is a prospective cohort that was established in 2015 with the goal to improve quality of care of EoE patients. The need for a national cohort was dictated by the rapid rise in EoE incidence all around the world and the lack of standardized care. From 2015 to 2020, the SEECs was embedded as a core project in the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) and benefitted from funding from the Swiss National Science Foundation (SNSF) [19]. Until then, the SEECs datacenter was located at the Institute of Social and Preventive Medicine of the University of Lausanne (IUMSP). The SEECs core team consisted of a study manager (C.S.), a questionnaire designer (E.S.), a biostatistician (J.B.R.), and the principal investigator (A.M.S.). The ending of the SIBDCS funding by the SNSF in December 2020 necessitated a multi-step re-organization of the SEECs. First, the datacenter was transferred from the IUMSP Lausanne to the Clinical Trials Unit of the

**Table 1.** Assessment of EoE activity in different domains (patient-reported outcomes (PRO) and physician-reported outcomes) stratified according to distinct frameworks

Domain	Randomized controlled trials	Observational studies	Daily clinical practice
Symptoms (adults)	DSQ, EEsAI PRO	EEsAI PRO	VAS
Quality of life (adults)	EoE-QoL-A	EoE-QoL-A	VAS
Endoscopic activity	EREFS	EREFS	EREFS
Histologic activity	EoE-HSS	Peak eosinophil count	Peak eosinophil count
Distensibility plateau (research tool)	EndoFLIP	EndoFLIP	EndoFLIP

DSQ, dysphagia symptom questionnaire; EEsAI PRO, Eosinophilic Esophagitis Activity Index PRO instrument; VAS, visual analog scale.

University of Bern (CTU Bern). Second, all SEECs data collected until December 2020 in Microsoft Access were transferred into REDCap<sup>®</sup> by the end of 2022, allowing fully electronic data capture. These different phases of the SEECs are shown in Fig. 1. Third, the SEECs biobank was transferred from the Institute of Pathology of the University of Bern to the Biobank of the Centre Hospitalier Universitaire Vaudois (CHUV).

Questionnaires regarding PROs (symptoms and quality of life), available in German, French, and English, are completed by patients. Physicians' questionnaires are in English and focus on clinician-reported outcomes (endoscopic and histologic activity). Until December 2020, data were manually collected using paper questionnaires and were then introduced into a Microsoft Access database located at IUMSP Lausanne. During the transition phase in 2021–2022, data were collected in parallel on paper and electronically using REDCap<sup>®</sup> [20]. REDCap<sup>®</sup> is a free, user-friendly web-based interface in the form of organizational server software, with a secure form of neutral data collection tool that was created in 2004 at Vanderbilt University, Nashville, Tennessee [20]. It meets the HIPAA (Health Insurance Portability and Accountability Act) standards. Its use does not require any background knowledge or technical experience and the program can be customized by each organization to meet local security policies to address features and functionalities needed by users [20]. REDCap<sup>®</sup> allows researchers to directly manage their projects through any browser or device after given access to the codebase. In the transition phase, paper questionnaires were progressively transformed into an electronic format in REDCap<sup>®</sup> by collaborators at CTU Bern. By using REDCap<sup>®</sup>, SEECs patients can now complete their questionnaires either during their medical visit or from home by email or with their smartphone using a QR code. Thanks to its branching logic, REDCap<sup>®</sup> allows for an easier filling process by guiding the patient from one question to another according to the initial answer.

The initial SEECs project was submitted to and approved by the leading institutional review board (IRB) of the canton of Vaud (CER-VD) (Protocol No. 148/15) and the documents were then sent to and approved by the other five IRBs (EKNZ, Bern, Geneva, EKOS, and Zurich) between 2015 and 2016. Switzerland consists of 26 cantons/districts with a total of 7 ethics committees (two in the French-speaking part, four in the German-speaking part, and one in the Italian-speaking part). Until now, the SEECs does not include patients from the Italian-speaking part of the country (Ticino). The CER-VD categorized the SEECs as category B with a minimal risk for potential harm due to the acquisition of bio-

samples (blood samples, esophageal biopsies). All included patients are covered by an insurance policy issued by CHUV, spanning the entire country's locations. Physicians as well as research nurses have been including EoE patients since January 2016.

#### Eligibility Criteria

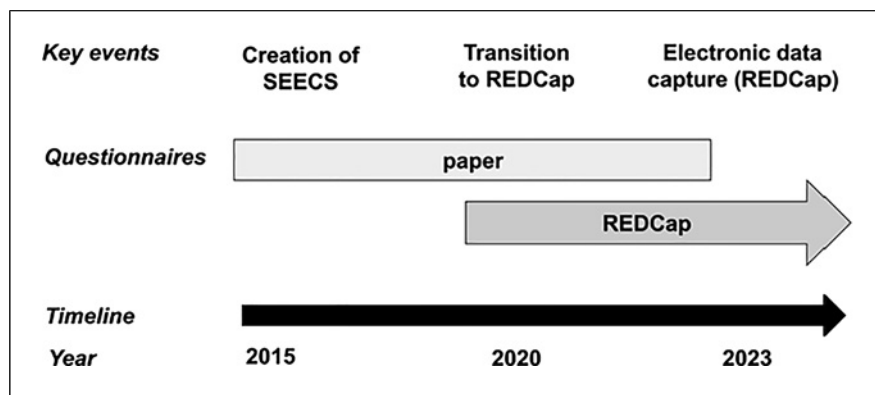
Patients are included in several EoE referral centers in French and German-speaking parts of Switzerland. The screening questionnaire assesses the eligibility of adult patients (age ≥18 years) based on the most recent guidelines [3, 4]. The EoE group's eligibility criteria are the presence of symptoms of esophageal dysfunction with a peak eosinophil count ≥15 eos/hpf in at least one high-power field (hpf) on esophageal biopsies, after excluding other potential causes of esophageal eosinophilia [3, 4]. As per the most recent consensus, the PPI trial is no longer a prerequisite for diagnosis and we combined the formerly called "PPI-REE" (PPI-responsive esophageal eosinophilia) subgroup with the EoE group. The GERD group comprises patients with a diagnosis of GERD (without concomitant EoE) according to the Lyon consensus [21]. Patients having both EoE and GERD are included in the EoE group since EoE is the "dominant" disease. Patients with GERD and esophagus-healthy controls are included as controls for research projects focusing on genetic characterization and translational research projects on esophageal barrier function.

The exclusion criteria are permanent residency outside Switzerland, patient/legal representative's refusal to sign the informed consent, and conditions other than EoE associated with esophageal eosinophilia. During endoscopies, if patients accepted, blood samples and esophageal biopsies are taken and stored in the CHUV biobank which also includes biosamples from esophagus-healthy controls and GERD patients. Blood is drawn from the venous access put in place for propofol sedation during endoscopy, then is filled in serum and EDTA tubes, allowing for later DNA sequencing.

#### Enrollment and Follow-Up Process

When an EoE patient is identified during a scheduled follow-up with the gastroenterologist, the inclusion process is explained. Upon agreement, the informed consent is signed with an additional consent form in case of agreement for the performance of genetic studies on biosamples. Consent forms consist of 3 sheets that need to be signed by both the patient and gastroenterologist (one sheet for the datacenter, one for the patient, and one for the patient's medical record). Moreover, patients provide their contact

**Fig. 1.** History of the Swiss EoE cohort (SEECs). Both paper-based questionnaires and REDCap were used during the transition phase between 2020 and 2022. From 2023 onward, data capture is fully electronic based on REDCap.



information with a signature and state whether they agree to be contacted during the year for additional questionnaires. The enrollment forms are then electronically completed in REDCap® by the study manager (CS). Patient recruitment is anonymous, and all questionnaires are labeled with unique 9-digit identifier tags in REDCap® with the identification key being stored in the data-center at CTU Bern.

Before the upper endoscopy, patients complete the RED-Capped EEsAI PRO and EoE-QoL-A questionnaire [22, 23]. During the endoscopy, at least 6 esophageal biopsies are taken (3 biopsies from the proximal and 3 from the distal esophagus, plus additional biopsies from lesions), fixed in formalin and sent to the local pathology institute to assess the grade and stage of fibro-inflammatory features. In case patients consented, two additional biopsies are taken for research purpose (1 from the proximal, 1 from the distal esophagus) and are stored in RNAlater Invitrogen® solution for RNA and protein stabilization. Biospecimens are then mailed to the CHUV biobank. After the endoscopy, physicians complete questionnaires focused on clinician-reported outcomes, including endoscopic (using EREFS) and histologic activity (using a modified EoE-HSS score that assesses peak eosinophil counts, eosinophil abscesses, basal layer hyperplasia, and subepithelial fibrosis) [24, 25].

Patients are usually seen once a year for a clinical, endoscopic, and histologic follow-up assessment unless dictated otherwise by clinical necessity. During these visits, follow-up questionnaires are filled in by the patient and the gastroenterologist. In case of an unscheduled event or an emergency visit for food impaction, follow-up questionnaires are also completed. Of note, assessment of PROs and clinician-reported outcomes is done all on the same day. Table 2 summarizes the variables captured by the SEECs questionnaires in REDCap®, the frequency of their collection as well as the persons who complete them. Figure 2 illustrates a patient's typical enrollment and follow-up schedule.

#### Scientific Collaborations

SEECs aims to foster clinical and translational research projects and be a platform notably for the young generation of physicians and scientists. Standard operating procedures (SOPs) have been created regarding the submission of scientific protocols which are reviewed by the SEECs scientific committee

(A.M.S., A.S., L.B., T.G., C.S.). These members meet virtually 3 times a year and once physically in Switzerland for a progress report. SEECs is open for project submission from any researcher interested in the field. Requests for SOPs and project templates can be sent upon request by email to the corresponding author. The time from the submitted project to the final decision is typically 1 month. Thanks to SEECs data, several MD master projects and MD thesis projects could be completed, and numerous papers were published in highly ranked journals. SEECs is the core project of the SNEGID, the Swiss Network for Eosinophilic Gastrointestinal Diseases and further information can be found on the SNEGID website (<https://www.snegid.ch>).

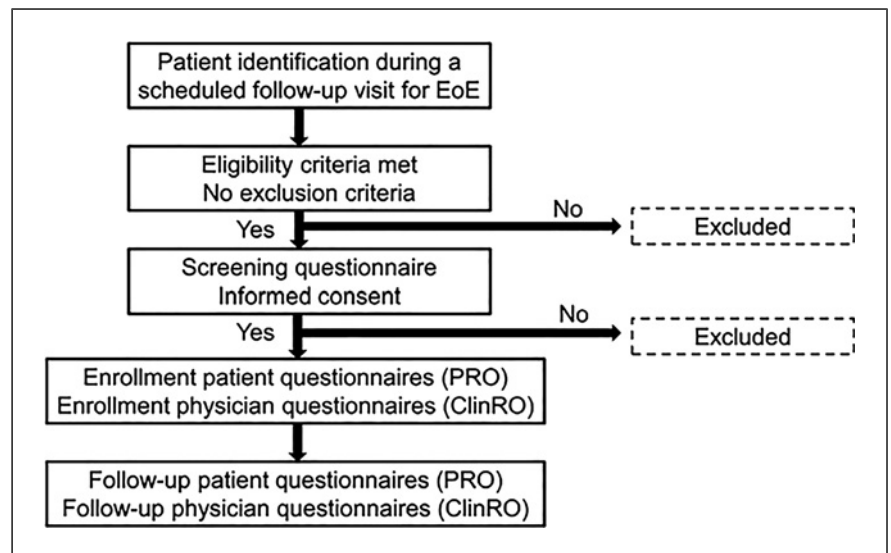
#### Results

Patients' recruitment process started in January 2016 and is ongoing. Despite the COVID-19 pandemic that impacted the healthcare system and led to the cancellation of many elective endoscopies, inclusions continued nevertheless. Figure 3 shows the number of patients with EoE included per year since January 2016. As of July 6, 2023, a total of 778 subjects were included in the cohort, of which 716 were EoE patients (92% of the cohort), 29 GERD patients (3.8%), and 33 esophagus-healthy controls (4.2%). The baseline characteristics of the cohort are detailed in Table 3. Concomitant GERD was found in 200 patients (27.9%) of the EoE group. Concomitant allergic disorders were found in 500 patients among 672 (74.4%) with EoE. At inclusion, 686 (95.8%) of EoE patients had ongoing treatment with 290 patients (42.3%) being on topical corticosteroids (either budesonide or fluticasone syrup), 281 patients (41%) on orodispersible budesonide tablets (Jorveza®), 162 patients (23.6%) on PPIs, 103 patients (15%) on elimination diets, while 166 patients (24.2%) had an esophageal dilation

**Table 2.** Variables captured by the SEECs questionnaires as well as the frequency of their completion

Variables	Questionnaires		Frequency of data collection		
	physician	patient	screening sheet	at inclusion	at follow-up
Inclusion/exclusion criteria			X	X	
Diagnosis	X		X	X	X
Clinical activity	X	X		X	X
Quality of life		X		X	X
Endoscopic activity of EoE	X			X	X
Stricture dilation	X			X	X
Endoscopic activity of concomitant GERD	X			X	X
Histologic activity of EoE	X			X	X
Blood eosinophilia	X			X	X
Current therapy for EoE	X			X	X
Current therapy for other atopic conditions	X			X	X
Global disease activity	X			X	X
Management decision	X			X	X
Past medical history	X			X	X
Past therapy for EoE	X			X	X
Clinical activity assessed monthly	X	X			X
Adverse events related to EoE drugs	X				X
New medical examinations	X				X
Complications related to EoE	X				X
Concomitant allergic disorders <sup>1</sup>	X	X		X	X
Family history of EoE/atopic disorders	X			X	X

EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease. <sup>1</sup>Concomitant asthma, rhinoconjunctivitis, eczema.

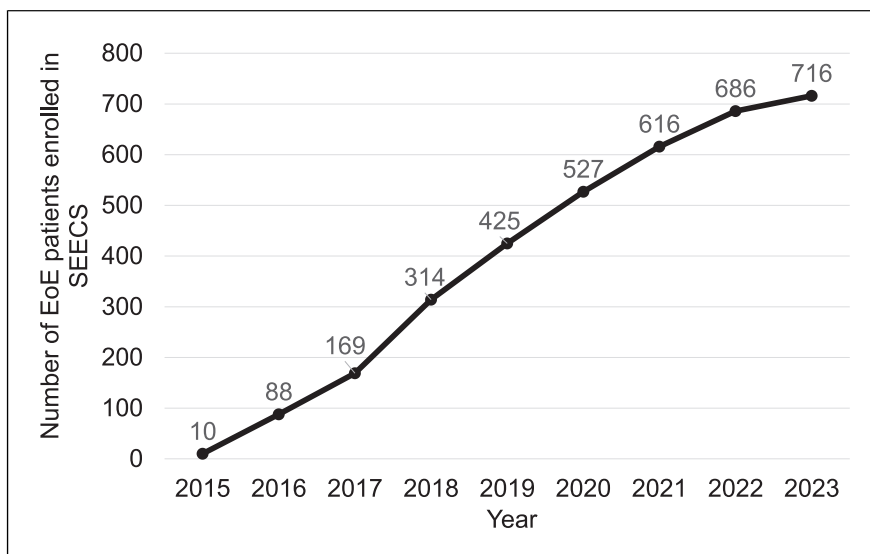


**Fig. 2.** Flowchart of patient enrollment and follow-up.

during the last visit. Twenty-nine patients (4.2%) were on topical corticosteroids for other conditions (asthma, allergic rhinitis). Some patients had off-label therapies as of July 2023 (6 patients under dupilumab, 4 patients participated in the phase III trial for cendakimab (blinded), 1 patient was treated with me-

polizumab and one with benralizumab). A total of 8,698 biosamples have been collected, of which 1,395 (16%) have been used in the framework of translational research projects (356 [26%] buffy coat samples; 173 [12%] plasma samples; 311 [22%] serum samples; and 555 [40%] esophageal biopsies).

**Fig. 3.** Cumulative numbers of patients with eosinophilic esophagitis included in the cohort between January 2016 and July 2023. SEECS, Swiss Eosinophilic Esophagitis Cohort Study.



**Table 3.** Baseline characteristics of the included subjects as of July 6, 2023

Characteristics	EoE	GERD	Esophagus-healthy controls
Subjects, <i>n</i> (%)	716 (92)	29 (3.8)	33 (4.2)
Sex, <i>n</i> (%)			
Male	530 (74)	16 (55.2)	13 (39.4)
Female	186 (26.0)	13 (44.8)	20 (60.6)
Age at enrollment, years, mean, SD	41.9 (12.9)	53.6 (16.4)	51.7 (17.2)
Diagnostic delay, months, mean, SD	89.6 (96.2)	NA	NA
Concomitant GERD	200 (27.9)	29 (100.0)	0
Concomitant allergies <sup>a</sup> , <i>n</i> (%)			
Any atopic disease	500 (74.4)	11 (68.8)	NA
Missing	44	13	NA
Rhinoconjunctivitis	370 (74.0)	9 (81.8)	NA
Nasal polyposis	7 (1.4)	0	NA
Asthma	229 (45.8)	7 (63.6)	NA
Neurodermitis	77 (15.4)	2 (18.2)	NA
Oral allergy syndrome	229 (45.8)	3 (27.3)	NA
Current therapies <sup>b</sup> , <i>n</i> (%)			
Any current therapy	686 (95.8)	26 (89.7)	0
PPI for EoE	162 (23.3)	0	0
PPI for GERD	173 (25.2)	26 (89.7)	0
Budesonide or fluticasone syrup	290 (42.3)	0	0
OBT (Jorveza <sup>®</sup> )	281 (41)	0	0
Elimination diets	103 (15)	0	0
Esophageal dilation <sup>c</sup>	166 (24.2)	0	0

EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; NA, not applicable; OBT, orodispersible budesonide tablet; PPI, proton-pump inhibitors. <sup>a</sup>For concomitant allergies, the percentages are based on the number of patients with any atopic disease. <sup>b</sup>A therapy is defined as “current” if it has a start date, but not a stop date; percentages are based on patients with at least one therapy. <sup>c</sup>Esophageal dilation at last visit.

## Discussion

### *Strengths and Limitations*

The SEECS has several strengths and also some limitations. SEECS is a national cohort of adult patients with EoE and inclusion is based on strict diagnostic criteria. Assessment of clinical and biologic disease activity is based on validated instruments designed specifically for EoE. SEECS operates now with fully electronic data capture which avoids transcription errors and facilitates data entry for patients and physicians. A critical point is that patient-reported outcomes and measures of biologic activity are all assessed on the same day. This stringent approach will help to better characterize the controversially discussed relationship between PRO and biologic activity. Follow-up information is typically captured every 12–18 months. Biosamples are collected not only from patients with EoE but also from patients with GERD and from controls with a healthy esophagus, which allows for group comparisons in the framework of translational research projects. Standard operating procedures for data collection, project submission and publications using SEECS data facilitate the collaboration of stakeholders. More than 20 scientific articles were published using SEECS data and several MD master projects and MD thesis projects were realized.

As a first limitation, the SEECS is not population based. Second, we currently do not include pediatric EoE patients based on the current lack of a broadly accepted pediatric PRO instrument in German and French and their limited number in Switzerland. Third, we do not include adults with EoE from the Italian-speaking canton of Ticino in southern Switzerland. As of December 2023, the canton of Ticino had 357,289 inhabitants, which corresponds to 4.0% of the entire Swiss population (8,927,007 as of December 2023).

### *Collaboration*

SEECS is open to scientific collaborations with clinicians and researchers all over the world. Researchers interested in collaborating with the SEECS can submit a standardized proposal for a scientific project. The template for submission of the project will be provided by the corresponding author upon email contact.

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## Statement of Ethics

The study protocol including all related questionnaires was reviewed and approved by the Local Ethics Committees at each of the participating sites (lead commission CER-VD, Approval No. 148-15). A protocol amendment was approved by CER-VD in July 2022 after REDCapping of questionnaires (PB\_2016\_01962 [148-15]). Patients provided their written informed consent to participate in this study.

## Conflict of Interest Statement

Jeanine Wakim has no relevant financial, professional, or personal relationships to disclose. Ekaterina Safroneeva reports (i) consulting fees from Avir Pharma, Inc., Aptalis Pharma, Inc., Celgene Corp., Novartis, AG, and Regeneron Pharmaceuticals Inc.; (ii) being an employee of Tillotts Pharma AG. Catherine Saner has no relevant financial, professional, or personal relationships to disclose. Jean-Benoit Rossel has no relevant financial, professional, or personal relationships to disclose. Sven Trelle has no relevant financial, professional, or personal relationships to disclose. Marcel Zwahlen has no relevant financial, professional, or personal relationships to disclose. Luc Biedermann received consulting fees and/or speaker fees and/or research grants from Adare/Ellodi Pharmaceuticals, Inc., AstraZeneca, AG, Switzerland, Receptos-Celgene-BMS, Dr. Falk Pharma, GmbH, Germany, Glaxo Smith Kline, AG, Nestlé S. A., Switzerland, Novartis, AG, Switzerland, and Regeneron-Sanofi Pharmaceuticals. Andrea Kreienbuehl has no relevant financial, professional, or personal relationships to disclose. Thomas Greuter received consulting fees and/or speaker fees and/or research grants from Adare/Ellodi Pharmaceuticals, Inc., AstraZeneca, AG, Switzerland, Receptos-Celgene-BMS, Dr. Falk Pharma, GmbH, Germany, Glaxo Smith Kline, AG, Nestlé S. A., Switzerland, Novartis, AG, Switzerland, and Regeneron-Sanofi Pharmaceuticals. Philipp Schreiner received consulting fees and/or speaker fees from Dr. Falk Pharma, GmbH, Takeda, Regeneron-Sanofi Pharmaceuticals, AbbVie, Janssen-Cilag, Receptos-Celgene-BMS. Peter Netzer has no relevant financial, professional, or personal relationships to disclose. Annett Franke has no relevant financial, professional, or personal relationships to disclose. Stephan Brand has no relevant financial, professional, or personal relationships to disclose. Chantal Hasler has no relevant financial, professional, or personal relationships to disclose. Patrick Aepli has no relevant financial, professional, or personal relationships to disclose. Emanuel Burri has no relevant financial, professional, or personal relationships to disclose. Achim Weber has no relevant financial, professional, or personal relationships to



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## Author Contributions

Jeanine Wakim El-Khoury and Ekaterina Safroneeva: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the

manuscript for important intellectual content. Catherine Saner: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; and administrative, technical, or material support. Jean-Benoit Rossel, Sven Trelle, Marcel Zwahlen, Luc Biedermann, Andrea Kreienbuehl, Philipp Scheiner, Peter Netzer, Annett Franke, Stephan Brand, Chantal Hasler, Patrick Aepli, Emanuel Burri, Achim Weber, Christine Sempoux, Ruggero Biral, Wolfram Jochum, Joachim Diebold, and Niels Willi: acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Thomas Greuter: acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtaining funding; and administrative, technical, or material support. Alex Straumann: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis. Alain M. Schoepfer: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtaining funding; administrative, technical, or material support; and study supervision.

## Data Availability Statement

The data that support the findings of this study are not publicly available as patients enrolled into SEECs did not consent to make their data publicly available. Requests for access to SEECs data in the framework of a clearly defined research project can be submitted to the corresponding author.

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