UCARE LEVELUP

NEWSLETTER 3
APRIL 2022

The Physician Education and Communication Program

Dear urticaria treating physician,

2022 is already in its second quarter and it is with great excitement that we bring you our third *LevelUp* newsletter looking back at the first quarter of 2022 and also looking forward to the next. The *LevelUp* program is continuously releasing new content and is educating physicians through its various formats.

In this newsletter we are extremely excited to tell you that the GA²LEN **C**hronic **U**rticaria **S**elf-**E**valuation APP, **CRUSE**® has been launched and we explore more on what it does, the advantages for physicians and patients and how to get it. We have a look back at the Urticaria Conference 2021 in Hiroshima, Japan and expand on some of the program's highlights. We get advised by some of most insightful physicians on treatment of Chronic Inducible Urticaria (CIndU). An overview of some active clinical trials is shared with the opportunity to get involved. We have an interview with Dr. Ivan Cherrez about PROMUSE and find out why he chose to do this study with UCARE. You can also gain real insight in looking at the latest research results including safety of Covid-19 vaccines, phase 1, 2 and 3 trials, prevention of hereditary angioedema attacks, treatment of inducible urticaria and much more.

We also update you on the latest happening in *LevelUp*, *4U* and the world of Urticaria. Enjoy the read, and please share this newsletter with your entire network. If you have not yet signed up for the newsletter and want to be invited to other *LevelUp* and *4U* events, please sign up here:

Sign up to the LevelUp Newsletter

Contact us: ucare-levelup@ga2len.berlin

GA²LEN Global Allergy and Asthma European Network
Network of Excellence

UCARE Urticaria Centers of Reference and Excellence
A GA²LEN NETWORK

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NOVARTIS Allakos

HOT TOPICS

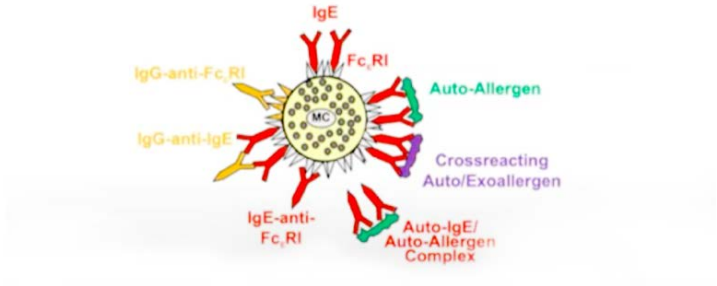
Urticaria Conference 2021, HIROSHIMA, JAPAN

by Dr. Bahar Sevimli Dikicier

The Urticaria Conference took place in Hiroshima, Japan, in December ; with 520 attendees from 45 countries taking part. The program was filled with scientific sessions, workshops and oral communications including the latest top developments, clinical trials and research. Leading experts and investigators as well as enthusiastic young researchers took the stage during the three-day program. Here is a brief summary highlighting the most exciting lectures and the latest news from the Urticaria Conference 2021:

Prof. Dr. Marcus Maurer's talk focused on the mast cells and IgE: the binding of IgE-anti-FCERI, IgG-anti-IgE, IgG-anti-FCERI to the FCERIs and driving autoimmune CSU (IgG) which is named Type IIb CSU. He also talked about the auto-allergic CSU (IgE) driven by the auto-IgE/ auto-allergen complexes, cross-reacting auto/ exo-allergen, and auto-allergen interaction with FCERI.

Figure 1:

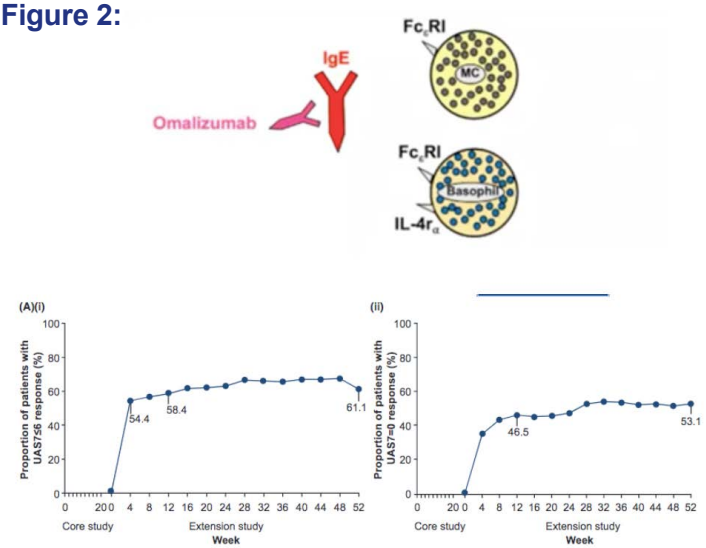


Autoimmune CSU (IgG) Type IIb (CSU)	Autoallergic CSU (IgE) Type I (CSU)

Prof. Dr. Romi Saini mentioned the possibility of mixed profiles: Autoimmune CSU (IgG) (Type IIb) and auto-allergic CSU (IgE)(Type I) may be present in the same patient. He also stated that the higher total IgE levels (more than 18 IU /ML) and the higher baseline basophil count and positive BHRA (basophil histamine release assay) is associated with higher response and vice versa with OMA treatment in CSU.

Prof. Dr. Jonathan A. Bernstein focused on how the eosinophil count is related with disease activity and response to OMA; and stated the findings supporting both the eosinophil infiltration in the skin and low baseline blood eosinophil counts are associated with high disease activity and low OMA response. When the eosinophil counts are high, the disease activity is low with a high response to OMA. He shared the promising results of Benralizumab, targeting IL-5 receptor on the eosinophils which showed achievement of primary end points of the phase II study in terms of lowering UAS. Prof. Dr. Allen Philip Kaplan reviewed the investigations of some new chemoattractant mediators and triggering the involvement of T helper cells and Th-17 cells, neutrophils, monocytes, and reacting with the endothelial cells which activates the coagulation cascade by tissue factor, and neuro-stimulation in the end, causing itch. Prof. Dr. Simon Francis Thomsen highlighted new biological treatments: Phase 2 studies with Ligelizumab 240 mg showed no new safety signals with significant clinical high and rapid efficacy, also phase 3 data will be available soon (FIGURE2). He also talked about ongoing phase 2 and 3 studies with dupilumab, mepolizumab, reslizumab and benralizumab each presenting promising results.

Figure 2:



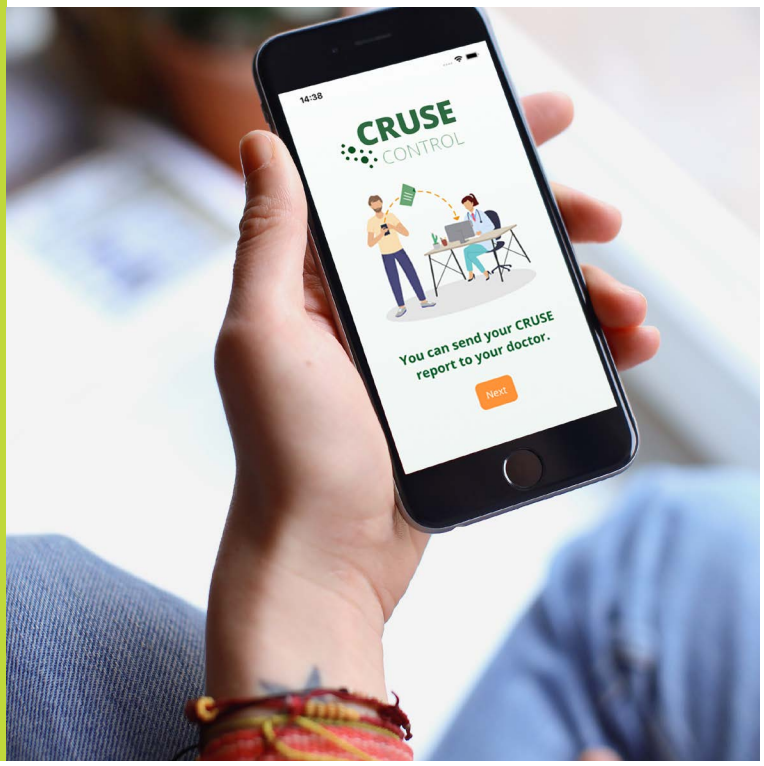
And finally Prof. Dr. Martin Metz talked about small molecules: BTK inhibitors (Fenebrutinib and Remibrutinib), SYK inhibitor (topical GSK2646264) for treatment of CSU. BTK inhibitors demonstrate significant decrease in UAS without safety concerns. Topical SYK inhibitor seems to be reducing the temperature threshold in cold urticaria in phase 1 studies.

YEAR END REVIEW - UCARE MEETING

CRUSE APP

CRUSE® app is bringing Urticaria monitoring to the 21st century

After extensive development and testing, GA²LEN UCARE, in association with Moxie and Peercode has launched its new mobile app, the **C**hronic **U**rticaria **S**elf-**E**valuation APP, CRUSE® in March 2022. Currently CRUSE® is available in Germany, Austria, Switzerland and the United Kingdom and will launch in Italy in Q2 of 2022 and will eventually be made available worldwide.

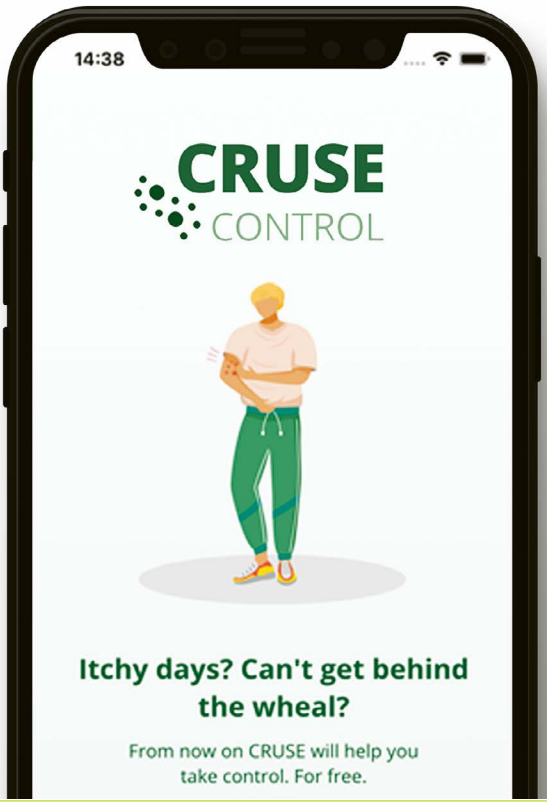


ABOUT THE CRUSE® APP

The APP is based on PROMs (Patient Reported Outcome Measures), which are well-known and widely used in everyday clinical practice. Incorporating them all into one app so that they work well in the end meant a lot of trial and error and has resulted in a fantastic user friendly experience.

CRUSE®'S ADVANTAGES FOR PATIENTS:

CRUSE® allows patients to record their urticaria symptoms and impact on their quality of life in just a few minutes each day.



Marcus Maurer, Sophia Neisinger and Anja Lingau spearheaded the app development and together with UCARE is making it available for physicians and patients to improve urticaria monitoring and treatment.

CRUSE®'S ADVANTAGES FOR PHYSICIANS:

Physicians can get a detailed long term view of how their patients respond to treatment. This is made possible by the reports generated by CRUSE® that patients can share with physicians. CRUSE® will also allow for data collection (all anonymized) like never before giving us a true understanding on how patients live with urticaria, how medication affects their quality of life and how treatment can be improved. CRUSE could become a "prescription app", i.e. a digital health application to assist physicians' patient care.

CRUSE®'S MISSION

CRUSE®'s mission is to become the biggest platform for patients with chronic urticaria worldwide. We can achieve this with the UCARE network's sheer size and experience. The aim is to utilize the CRUSE® app as the exclusive digital tool for all UCARE centers to assess patients' disease activity and control.

To get the app simply scan the QR code:

CRUSE app

RESEARCH AND RESULTS
by Prof. Michael Rudenko

Safety of COVID-19 vaccines

LINK TO ARTICLE

The reactogenicity of the vaccines including pain, redness, **urticaria**, and swelling at the site of the injection was reported in 34.56% of the participants. ... This study is aimed to identify the adverse effects associated with three types of coronavirus disease 2019 vaccines. Approximately 1736 individuals agreed to participate in this study. The duration and severity of adverse effects were not affected by age or gender. Unusual side effects should be closely monitored to establish determine they are linked to the immunization.

Al Khames Aga QA, Alkhaffaf WH, Hatem TH, Nassir KF, Batineh Y, Dahham AT, Shaban D, Al Khames Aga LA, Agha MYR, Traqchi M. J Med Virol. 2021 Dec;93(12):6588-6594. doi: 10.1002/jmv.27214. Epub 2021 Jul 28.PMID: 34270094 Free PMC article. Clinical Trial.

Fenebrutinib in H(1) antihistamine-refractory chronic spontaneous urticaria: a randomized phase 2 trial.

LINK TO ARTICLE

Bruton's tyrosine kinase (BTK) is crucial for FcepsilonRI-mediated mast cell activation and essential for autoantibody production by B cells in chronic spontaneous urticaria (CSU). Fenebrutinib, an orally administered, potent, highly selective, reversible BTK inhibitor, … This double-blind, placebo-controlled, phase 2 trial (EudraCT ID 2016-004624-35) randomized 93 adults with antihistamine-refractory CSU to 50 mg daily, 150 mg daily and 200 mg twice daily of fenebrutinib or placebo for 8 weeks.

Metz M, Sussman G, Gagnon R, Staubach P, Tanus T, Yang WH, Lim JJ, Clarke HJ, Galanter J, Chinn LW, Chu T, Teterina A, Burgess T, Haddon DJ, Lu TT, Maurer M. Nat Med. 2021 Nov;27(11):1961-1969. doi: 10.1038/s41591-021-01537-w. Epub 2021 Nov 8.PMID: 34750553 Free PMC article. Clinical Trial.

Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial.

LINK TO ARTICLE

APeX-2 was a double-blind, parallel-group study that randomized patients at 40 sites in 11 countries 1:1:1 to receive once-daily berotralstat in a dose of 110 mg or 150 mg or placebo. Both the 110-mg and 150-mg doses of berotralstat reduced HAE attack rates compared with placebo and were safe and generally well tolerated. The most favorable benefit-to-risk profile was observed at a dose of 150 mg per day.

Zuraw B, Lumry WR, Johnston DT, Aygören-Pürsün E, Banerji A, Bernstein JA, Christiansen SC, Jacobs JS, Sitz KV, Gower RG, Gagnon R, Wedner HJ, Kinaciyan T, Hakl R, Hanzlíková J, Anderson JT, McNeil DL, Fritz SB, Yang WH, Tachdjian R, Busse PJ, Craig TJ, Li HH, Farkas H, Best JM, Clemons D, Cornpropst M, Dobo SM, Iocca HA, Kargl D, Nagy E, Murray SC, Collis P, Sheridan WP, Maurer M, Riedl MA. J Allergy Clin Immunol. 2021 Jul;148(1):164-172.e9. doi: 10.1016/j.jaci.2020.10.015. Epub 2020 Oct 21.PMID: 33098856 Free article. Clinical Trial.

Acetylcholine-induced whealing in cholinergic urticaria - What does it tell us?

LINK TO ARTICLE

BACKGROUND: Cholinergic urticaria (CholU) is characterized by the occurrence of itchy wheals induced by sweating. ... Intradermal ACh testing does not allow for the identification of CholU patients due to its low sensitivity. ACh-induced wheals, in patients with CholU, is linked to sweating and longer lasting symptoms. Intradermal ACh testing is an interesting tool for mechanistic studies in CholU.

Altrichter S, Wang Y, Schumacher P, Alraboni O, Church MK, Maurer M. J Dermatol Sci. 2021 Jul;103(1):10-15. doi: 10.1016/j.jdermsci.2021.05.001. Epub 2021 May 7.PMID: 34049770 Clinical Trial.

A randomized controlled trial of adding intravenous corticosteroids to H1 antihistamines in patients with acute urticaria.

LINK TO ARTICLE

BACKGROUND: Acute urticaria is a common dermatological condition in emergency departments (EDs). ...CONCLUSIONS: The present study did not find evidence that adding IV dexamethasone improves the treatment of severe pruritus from uncomplicated acute urticaria. The present study did not find evidence that adding IV dexamethasone improves the treatment of severe pruritus from uncomplicated acute urticaria. Oral corticosteroid therapy may be associated with persistent urticaria activity. Due to the lack of clinical benefits and the potential for side effects, using corticosteroids as an adjunctive treatment is discouraged.

Palungwachira P, Vilaisri K, Musikatavorn K, Wongpiyabovorn J. Am J Emerg Med. 2021 Apr;42:192-197. doi: 10.1016/j.ajem.2020.02.025. Epub 2020 Feb 19.PMID: 32139204 Clinical Trial.

Effect of omalizumab treatment on peripheral nerves in patients with chronic spontaneous urticaria.

LINK TO ARTICLE

AIM: Chronic spontaneous urticaria (CSU) is characterised by itchy, red and raised lesions that appear as an attack without any cause and last for six weeks or longer. It can be considered that omalizumab has no effect on peripheral nerves, and it is a safe and well tolerated agent in terms of both peripheral nerves and neurological structure.

Altunisik E, Inan Dogan E. Cutan Ocul Toxicol. 2021 Jun;40(2):130-134. doi: 10.1080/15569527.2021.1914076. Epub 2021 Apr 26.PMID: 33902373 Clinical Trial.

Effects of a topical treatment with spleen tyrosine kinase inhibitor in healthy subjects and patients with cold urticaria or chronic spontaneous urticaria: Results of a phase 1a/b randomised double-blind placebo-controlled study.

LINK TO ARTICLE

METHODS: Healthy volunteers (HV) with a positive allergen skin prick test received GSK2646264 (0.5% or 1% ww) and placebo creams on up to 10% body surface area (BSA). Cold (ColdU) or chronic spontaneous (CSU) urticaria patients received 1% GSK2646264 or placebo. This Phase 1/1b study confirms that GSK2646264 cream applied topically penetrates the skin and some reduction in critical temperature threshold was observed.

Dickson MC, Walker A, Grattan C, Perry H, Williams N, Ratia N, Dewit O, Gisbert S, Metz M, Maurer M. Br J Clin Pharmacol. 2021 Dec;87(12):4797-4808. doi: 10.1111/bcp.14923. Epub 2021 Jun 18.PMID: 34020509 Clinical Trial.

How bilastine is used to treat allergic rhinitis and urticaria in children.

LINK TO ARTICLE

Management guidelines for allergic rhinitis and urticaria recommend oral second-generation antihistamines as first-line treatment. ...In this article, evidence is reviewed for use of bilastine in children with allergic rhinoconjunctivitis or urticaria.

Rodríguez Del Río P, Rodríguez Fernández F, Ballester Asensio E, Tortajada-Girbés M. Immunotherapy. 2022 Jan;14(1):77-89. doi: 10.2217/imt-2021-0251. Epub 2021 Dec 1.PMID: 34850647 Clinical Trial.

TREATMENT ADVICE

Treatment of Chronic Inducible Urticaria (CIndU)

by Dr. Emek Kocatürk

Chronic inducible urticaria (CIndU) is the type of urticaria which require a trigger for the wheals to come out. The individual wheal typically last shorter than spontaneous urticaria (except delayed pressure urticaria) but the disease tends to show a longer duration than spontaneous urticaria and the quality of life is impaired substantially due to requirement of restrictions from eg cold, hot, sweating activities etc.

The international guidelines on urticaria recommend adopting the same treatment algorithm for the management of CIndU (1,2). As with chronic spontaneous urticaria, the first step of treatment is starting with a standard dose of second generation H1 antihistamine (sg-AHs) and stepping up to four-fold in case of no response. The rates of response to treatment with antihistamines change depending on the type of CIndU. For symptomatic dermographism (SD) and cholinergic urticaria (Cho-U) sg-AHs are beneficial while cold urticaria (Cold-U) requires higher doses and delayed pressure urticaria (DPU) may show resistance to treatment with sg-AHs (2,3).

A recent meta-analysis showed addition of H2-blockers might provide benefit in SD patients (4) while another showed leukotriene antagonists might improve symptoms in DPU (5).

In general, CIndU patients who are refractory to treatment with antihistamines, although off-label, evidence on the use of omalizumab is increasing. There are placebo-controlled trials on the efficacy of omalizumab in SD, Cho-U and Cold-U. Real life evidence on the use of omalizumab in many types of CIndU is cumulating and showing response rates ranging between 45.5%-100%. DPU, SDand Cold-U have the best responding rates, while Cho-U response rates are lower than the other types (6).

Other options for treatment in omalizumab refractory cases change based on the type of CIndU. Cyclosporine has been shown effective in case series in SD patients and solar urticaria, while dapsone is an option for DPU and danazol might be helpful in Cho-U patients who are refractory (2). UV hardening therapy and afamelanotide for solar urticaria, doxycycline and ketotifen for cold-urticaria and phototherapy for SD are other options that have provided some benefit in refractory cases (3).

REFERENCES:

1. Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022 Mar;77(3):734-766.
2. Magerl M, Altrichter S, Borzova E, Giménez-Arnau A, Grattan CE, Lawlor F, Mathelier-Fusade P, Meshkova RY, Zuberbier T, Metz M, Maurer M. The definition, diagnostic testing, and management of chronic inducible urticarias - The EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy. 2016 Jun;71(6):780-802.
3. Dressler C, Werner RN, Eisert L, Zuberbier T, Nast A, Maurer M. Chronic inducible urticaria: A systematic review of treatment options. J Allergy Clin Immunol. 2018 May;141(5):1726-1734.
4. Kulthanan K, Ungprasert P, Tuchinda P, Chularojanamontri L, Rujitharanawong C, Kiratiwongwan R, Jantanapornchai N, Hawro T, Maurer M. Symptomatic Dermographism: A Systematic Review of Treatment Options. J Allergy Clin Immunol Pract. 2020 Oct;8(9):3141-3161.
5. Kulthanan K, Ungprasert P, Tuchinda P, Chularojanamontri L, Charoenpipatsin N, Maurer M. Delayed Pressure Urticaria: A Systematic Review of Treatment Options. J Allergy Clin Immunol Pract. 2020 Jun;8(6):2035-2049.e5.
6. Can PK, Salman A, Hoşgören-Tekin S, Kocatürk E. Effectiveness of Omalizumab in Patients with Chronic Inducible Urticaria: real-life experience from two UCARE centres. J Eur Acad Dermatol Venereol. 2021 Oct;35(10):e679-e682.

PROJECTS

PROMUSE

An interview with:
Dr. Ivan Cherrez

Interview by:
Dr. Rabia Oztas Kara

Could you briefly explain what PROMUSE is?
PROMUSE is an academic work initiated by Respiralab Research Group in Ecuador and is focussed on knowledge, perceptions, and limitations of the use Patient-Reported Outcomes Measures (PROMs) by physicians in allergic diseases.

What are your objectives for starting this project, and why is it performing under the umbrella of UCARE network?
The main objective is to describe the knowledge, perceptions, and limitations of the use of PROMs by physicians in allergic diseases in order to increase engagement and uptake of these tools in clinical practice.

Secondary objectives are to:

- Develop a questionnaire that evaluates knowledge, perceptions, and limitations of physicians in the use of PROMs in urticaria, angioedema, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, rhinosinusitis and asthma;
- Describing the factors that influence PROs data interpretation or use in clinical practice
- Identifying what PROs have the most utility for healthcare professionals during their daily clinical practice according to the specific disease studied.
- The GA2LEN UCARE network enables excellent support for such a global study as it connects the best global urticaria experts.

Who are the steering committee members?
Ivan Cherrez Ojeda is the principal investigator and study chairman, and other steering committee members are Marcus Maurer, Torsten Zuberbier, and Jean Bousquet.

How are you managing to do a study with so many centers?
To achieve the proposed objectives when determining clinicians' perspectives on PROMs, a cross-sectional, anonymous study is carried out using a survey-type questionnaire that is sent in electronic format to the participating physicians.

What challenges may healthcare professionals faced when interpreting the meaning and implications of PROs data?
The challenges may arise due to the variation by which PRO data are used, scored, and reported. Methods for optimizing the feedback of PRO data to healthcare professionals are an emerging field of research. Currently, little is known about the best methods for providing summarised PROs data in a way that is meaningful for healthcare providers.

To the best of our knowledge, there is currently little empirical evidence available to support best practice in the feedback methods for PROs data, particularly at the health service level. That is why this study aims to identify clinicians' perspectives regarding the use of PROMs in clinical contexts.

Clinical Trials

by Dr. Sergio Dortas Jr.

CLINICAL TRIAL

Trial to Assess the Efficacy and Safety of LEO 152020 in Adult Patients with Cholinergic Urticaria

IDENTIFIER: NCT04853992

This is a phase 2a, randomised, double-blind, placebo-controlled, cross-over trial conducted in Germany at 3-6 sites to assess the efficacy of LEO 152020. LEO 152020 is a small drug molecule which can bind to the histamine 4 receptor (H4R). LEO 152020 is a tablet for oral administration. Subjects will be randomised to one of two treatment sequences (A and B). Each treatment period will last 7 days with a wash-out period of 7 days between treatments. Half of the subjects will start with treatment A followed by treatment B while the other half will start with treatment B followed by treatment A. A safety follow-up visit will be performed 3 days after last dose of the tested medication.

CLINICAL TRIAL

A Study to Investigate the Use of Benralizumab in Patients with Chronic Spontaneous Urticaria Who Are Symptomatic Despite the Use of Antihistamines (ARROYO)

IDENTIFIER: NCT04612725

The aim of this study is to investigate the use of benralizumab (an IL-5 inhibitor) as treatment for patients with chronic spontaneous urticaria (CSU) who are symptomatic despite the use of antihistamines. It is proposed that benralizumab will deplete eosinophils and basophils from affected skin, improve symptoms of CSU, and improve CSU-related quality of life. This Phase 2b study is designed to evaluate induction and maintenance dosing regimens.

CLINICAL TRIAL

Dupilumab for the Treatment of Chronic Inducible Cold Urticaria in Patients Who Remain Symptomatic Despite the Use of H1-antihistamine (LIBERTY-CINDU CUrIADS)

IDENTIFIER: NCT04681729

The aim of this study is to investigate the use of benralizumab (an IL-5 inhibitor) as treatment for patients with chronic spontaneous urticaria (CSU) who are symptomatic despite the use of antihistamines. It is proposed that benralizumab will deplete eosinophils and basophils from affected skin, improve symptoms of CSU, and improve CSU-related quality of life. This Phase 2b study is designed to evaluate induction and maintenance dosing regimens.

LevelUp and 4U Activities

By Dr. Iman Nasr and Reinhardt Britz

LEVELUP WEBINARS

The third webinar in our UCARE LevelUp series was “Year End Review / UCARE Meeting” launched on January 26th, 2022 was a great success. It focused on the UCARE2021 Conference in Hiroshima, Japan, one of the biggest and most important urticaria meetings of 2021, featuring sessions on new insights on the pathogenesis, the differential diagnosis, and the management approach to urticaria as well as on new results from basic scientific projects and epidemiological studies on chronic urticaria. New treatment approaches and the results of clinical studies in chronic urticaria also played a big part in the conference. This webinar gave a brief overview of the individual conference sessions. Moreover, speakers shared their critical look on the topics that were featured during the conference.

To see our webinar videos scan or click on the QR code.

UCARE LevelUp

LEVELUP PODCASTS

PODCAST

"All Things Urticaria" is the podcast series that is available on demand and has been made possible in cooperation with our Program Sponsors, network experts, scientists and medthority. There are 38 Episodes so far and further episodes are constantly being created touching on various types and aspects of urticaria.

UCARE 4U WEBINARS

The UCARE 4U webinars for patients have also kicked off with the firsrt webinar focussing on what Urticaria is and the second about focussing on Covid-19 and urticaria. The Webinars have been broken down into smaller parts that are easier to watch, and we are busy adding subtitles in many languages to make it accessible to all our network patients. The first parts that are available on demand by scanning or clicking the QR Code:

4U Content

UCARE 4U WEBSITE

The UCARE 4U website taskforce has finalised the website content for patients with urticaria. It will contains rich information for patients suffering with this condition. The website is expected to be launched mid-May and will be reachable at: www.ucare-4u.com

JOURNAL CLUBS

have taken place and will continue taking place every 2 weeks.

EVENTS

Upcoming Events

5 May 2022 18:00 (CEST)
4U webinar 3 - Different types of induced urticaria

SIGN UP HERE

16 June 2022 18:00 (CEST)
4U webinar 4 - Diagnostic procedure how to prepare

SIGN UP HERE

01-03 July 2022
EAACI Hybrid Congress 2022 In Prague

FIND OUT MORE

11-13 July 2022
10th EMBRN International Mast Cell and Basophil Meeting

FIND OUT MORE

07-10 September 2022
EADV Congress in Milan

FIND OUT MORE

14-15 September 2022
BRADYKININ SYMPOSIUM 2022 and Charité/ACARE ANGIOEDEMA SCHOOL 2022

FIND OUT MORE

7-8 December 2022
6th GA²LEN Global Urticaria Forum 2022 (GUF)

FIND OUT MORE

Connect with GA²LEN and UCARE on our social media pages by scanning this QR Code with you mobile phone or or by clicking on it.

Find our more

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Network of Excellence

We would like to thank our Taskforce members that worked on distilling the multitude of information out there into the second LevelUp newsletter: Bahar Sevimli Dikicier, Emek Kocatürk, Iman Nasr, Sérgio Dortas Junior, Roberta Fachini Jardim Criado, Michael Rudenko, Reinhardt Britz and the UCARE team.