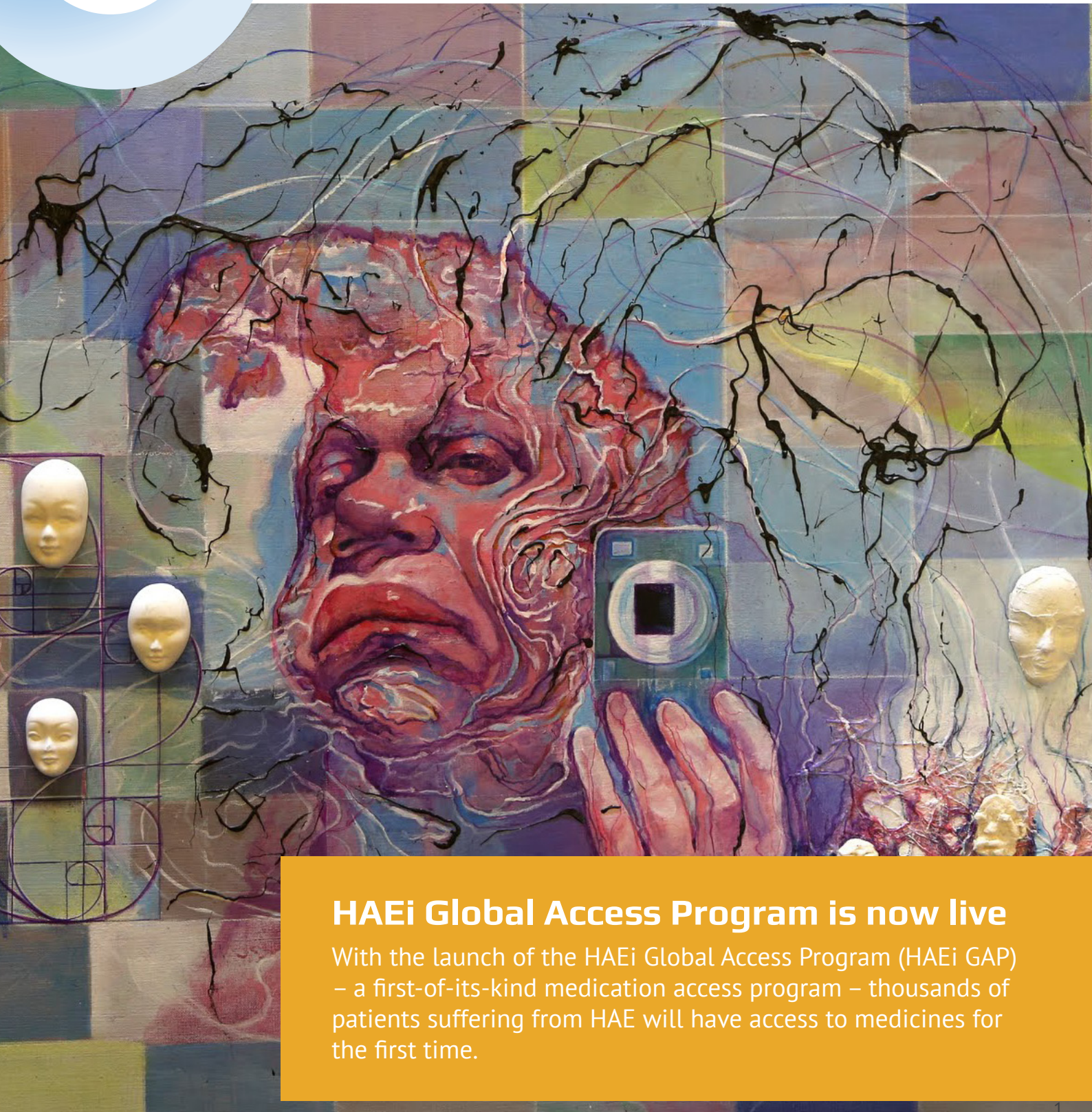
Issue 5 · September 2015

HAEi Newsletter



HAEi Global Access Program is now live

With the launch of the HAEi Global Access Program (HAEi GAP) – a first-of-its-kind medication access program – thousands of patients suffering from HAE will have access to medicines for the first time.

Tabel of Content

HAEi

HAEi is a global non-profit umbrella organization dedicated to working with its network of national HAE member organizations to raise awareness of HAE.

HAEi Newsletter · Issue 5 · September 2015

Front page photo by Tamás Thaler from the 9th C1 Inhibitor Deficiency Workshop in Budapest, May 2015

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HAEi is registered as a non-profit/charitable organization in Switzerland

A Message from the President

Dear HAEi Friends,

I hope this 5th HAEi newsletter of the year finds everyone happy and in good health. It is hard to believe that we are fast approaching the fourth quarter of 2015. HAEi plans to finish the year the same way we started it – by leading a global advocacy movement that strives to improve HAE patients' lives through broadening access to the HAE diagnosis and suitable therapies.

We are building off the momentum created by the launch of our Global Access Program as we implement an exciting variety of initiatives. Patient identification is the lifeblood of growing the global HAE community. With this in mind, we are focusing on creative ways to help member organizations enhance their ongoing outreach programs for finding new patients and helping undiagnosed patients obtain the appropriate testing. Other activities that will round out 2015 and take us into 2016 (to mention just a few) include

- engaging the HAEi Executive Committee in drafting a patient oriented "HAE Standards of Care" document for the global community,
- developing a prototype advocacy campaign that member organizations can use to communicate the remarkable impact modern HAE medicines have on saving lives and reducing the burden of illness,
- working with member organizations to identify local experts who can provide expert guidance to enhance access and reimbursement advocacy efforts directed at health ministries and regulatory authorities, and
- organizing regional workshops in areas where there are newer HAE members and limited or no access to medicines.

Finally, we have already begun intensive planning for our 2016 HAE Global Conference. We kindly ask HAEi friends to mark their calendars for this exciting event, which will take place on 19-22 May 2016 in Madrid, Spain.

HAEi cares deeply about the health and well being of every patient in our community. Please do not hesitate to contact us at info@haei.org for any reason.

Warmest regards,

Anthony J. Castaldo
President, HAEi

Trials recruiting patients

According to the International Clinical Trials Registry Platform under World Health Organization (WHO) and clinicaltrials.gov under the U.S. National Institutes of Health the following trials are recruiting patients:

First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of BCX7353 in Healthy Volunteers

Recruiting in United Kingdom

https://clinicaltrials.gov/ct2/show/study/NCT02448264

Pathogenesis of Physical Induced Urticarial Syndromes.

Recruiting in USA.

https://clinicaltrials.gov/ct2/show/NCT00887939

Safety of Ruconest in 2-13 Year Old HAE Patients.

Recruiting in Germany, Israel, Italy, Macedonia, Poland, and Romania.

https://clinicaltrials.gov/ct2/show/NCT01359969

Firazyr® Patient Registry Protocol (Icatibant Outcome Survey - IOS).

Recruiting in Austria, Brazil, Denmark, France, Germany, Greece, Ireland, Israel, Italy, Spain, Sweden, and United Kingdom.

https://clinicaltrials.gov/ct2/show/NCT01034969

Screening Protocol for Genetic Diseases of Mast Cell Homeostasis and Activation.

Recruiting in United States.

https://clinicaltrials.gov/ct2/show/NCT00852943

12-Week Safety and Efficacy Study of BCX4161 as an Oral Prophylaxis Against HAE Attacks OPuS-2.

Recruiting in Belgium, Canada, France, Germany, Hungary, Italy, United Kingdom, and USA.

http://clinicaltrials.gov/show/NCT02303626

Safety and Efficacy Study of CINRYZE for Prevention of Angioedema Attacks in Children Ages 6-11 with HAE.

Recruiting in Argentina, Germany, Italy, Mexico, Romania, United Kingdom, and USA.

http://clinicaltrials.gov/show/NCT02052141

A European Post-Authorisation Observational Study Of Patients With HAE.

Recruiting in France, Germany, Spain, and United Kingdom.

http://clinicaltrials.gov/show/NCT01541423

C1 Inhibitor Registry in the Treatment of HAE Attacks.

Recruiting in the Netherlands.

http://clinicaltrials.gov/show/NCT01397864

A Pharmacokinetic, Tolerability and Safety Study of Icatibant in Children and Adolescents With HAE.

Recruiting in Argentina, Australia, Austria, Canada, Colombia, Germany, Hungary, Israel, Italy, Spain, and USA.

http://clinicaltrials.gov/show/NCT01386658

Study to Assess the Tolerability and Safety of Ecallantide in Children and Adolescents With HAE.

Recruiting in USA.

http://clinicaltrials.gov/show/NCT01832896

Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in HAE Subjects.

Recruiting in Italy, Jordan, and USA.

http://clinicaltrials.gov/show/NCT02093923

A Study to Evaluate the Long-term Clinical Safety and Efficacy of Subcutaneously Administered C1-esterase Inhibitor in the Prevention of HAE.

Recruiting in USA.

https://clinicaltrials.gov/ct2/show/NCT02316353

A Phase 2 HAE Prophylaxis Study With Recombinant Human C1 Inhibitor.

Recruiting in the Netherlands.

https://clinicaltrials.gov/ct2/show/NCT02247739

An Open-Label Study of Icatibant in Japanese Subjects with Acute Attacks of HAE.

Recruiting in Japan.

http://www.shiretrials.com/sitecore/content/studies/clinicaltrialsen/2015/05/14/06/44/shp-fir-301?sc_lang=en

This trial is not yet recruiting but is expected to be so later on in 2015:

HAE, Neurobiology and Psychopathology.

Will be recruiting in Italy.

https://clinicaltrials.gov/ct2/show/NCT02159430

HAEi GAP GLOBAL ACCESS PROGRAM

HAEi Global Access Program

With the launch of the HAEi Global Access Program (HAEi GAP) – a first-of-its-kind medication access program – thousands of patients suffering from HAE will have access to medicines for the first time.

As you are probably already aware, we announced the HAEi Global Access Program (HAEi GAP) on **hae day :-)** this year, and the program "went live" on 21 July 2015.

Based on great commitment and huge efforts by both Clinigen Group and Pharming Group, Ruconest® is now available through the HAEi GAP.

Physicians who live in a country where Ruconest® is not commercially available can request access to Ruconest® for their patients through the HAEi GAP.

Please read more about the HAEi GAP and how to get access to life saving HAE medication on our website by following this link:

http://haei.org/hae/global_access_program/

Remember all requests for access to medicine through the HAEi GAP have to be initiated by a physician. We therefore advise interested HAEi friends to see their physician to discuss how you best can get access to the program. In addition, please feel free to contact HAEi should you have any questions.

HAE Global Conference in Madrid

Following our previous two successful HAE Global Conferences (2012 in Copenhagen, and 2014 in Washington DC), HAEi announced the 2016 HAE Global Conference to take place in Madrid, Spain on 19-22 May 2016.

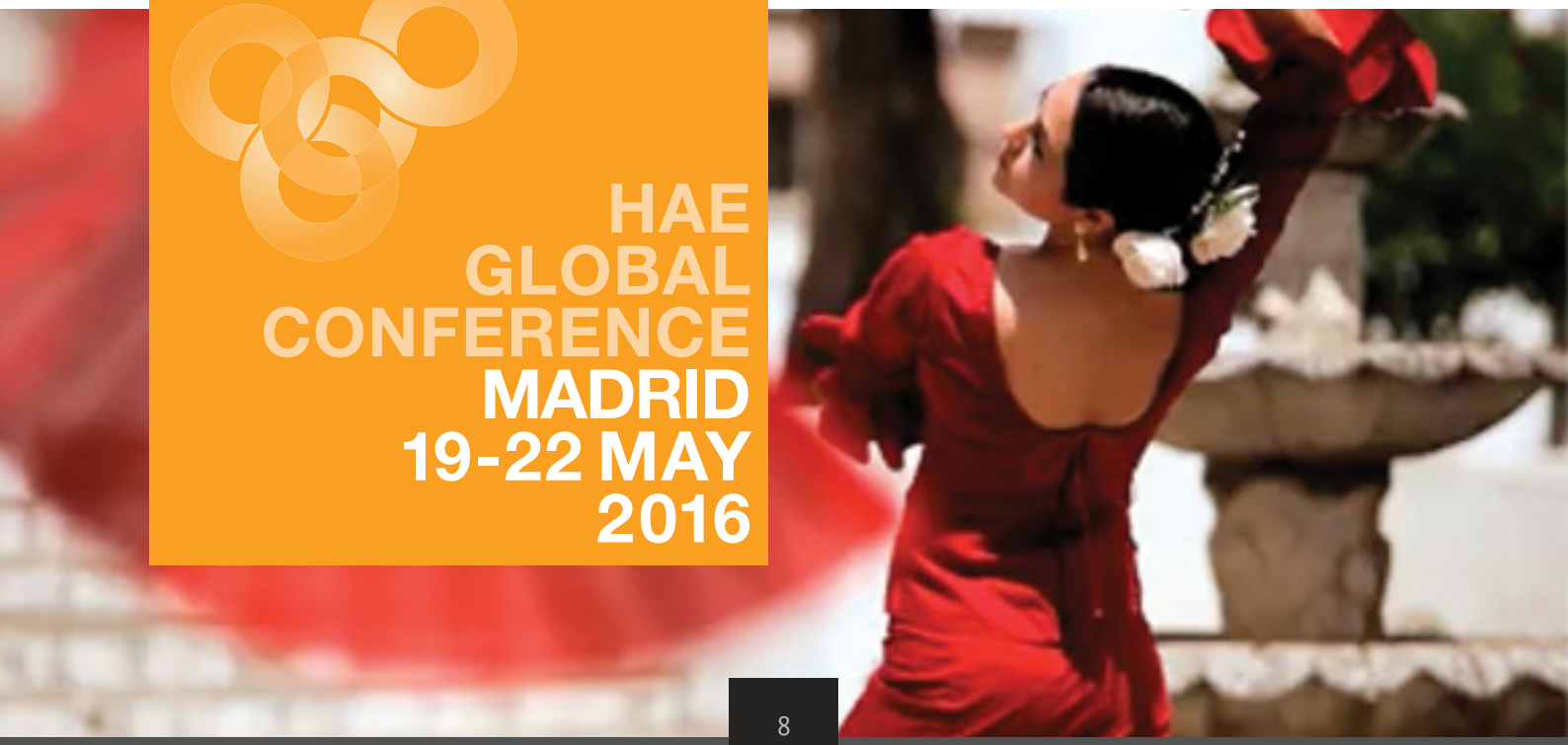
Attendees at the 2016 HAE Global Conference can expect a wide variety of important information and learning opportunities that include HAE fundamentals, the most recent clinical advances and consensus treatment recommendations, and advocacy strategies/ techniques for gaining or broadening access to HAE medicines. There will be a separate track for young patients that will enable peer group interaction and sharing of insights on how to cope with HAE. Health care professionals will also be an integral part of the conference. We will offer an educational and networking session for nurses specializing in HAE; and HAE physician/researchers from throughout the globe will gather to present abstracts and discuss future research opportunities.

As usual, the HAE Global Conference offers a blend of work and social/networking opportunities. The Scientific Program Committee and HAEi Executive Committee meetings will take place on Thursday 19 May 2016 in the afternoon. The nurses' session and HAE youngster track will take place on Thursday evening. The HAE youngsters will continue on Friday during the day. Conference sessions and exhibitions will run all day Friday 20 May ending with a Spanish tapas reception for all delegates. Conference sessions and exhibitions will continue on Saturday 21 May and the official conference sessions will end with a special dinner on Saturday evening. Sunday morning is reserved for an organized excursion or sightseeing tour of Madrid.

It is expected that the conference will be attended by approximately 550-600 delegates – including patients, care givers, physician/ researchers, other healthcare professionals, and industry representatives – from all over the world.

As with the previous two HAE Global Conferences we are currently working on a very attractive travel grant program for patients and their relatives (care givers), who are members a) of the HAEi family, and b) of one of our member organizations. We expect to be able to announce more details about the program and the registration process in October or November this year.

Announcements of the registration process will take place through this newsletter as well as on Facebook, LinkedIn and Twitter.



Ask the doctors

Physician/Scientists at the US HAEA Angioedema Center at the University of California San Diego field questions and the answers are posted on Facebook pages for Angioedema Center Facebook Page and the US HAEA. The answers are provided by expert physicians, Dr. Sandra Christiansen, Dr. Marc Riedl, and Dr. Bruce Zuraw. Here is what we believe is a highly relevant recently asked question.

Should HAE patients use more than one medication to treat attacks? What about recurring attacks after treatment? Given the multiple treatments for acute attacks of HAE do we need to use more than one of the medications? What happens if I have recurrent, continued swelling after a treatment?

Dr. Christiansen: It is indeed fortunate to have an array of choices for 'on demand' treatment of acute attacks. We now have four approved effective products: 1) Kalbitor an inhibitor of the enzyme plasma kallikrein which is responsible for generation of bradykinin which drives the vascular leak and swelling, 2) Firazyr which blocks the receptor or 'docking site' for bradykinin on the vascular epithelium, 3) Berinert which is a plasma derived C1 inhibitor which can arrest the swelling by inhibiting activation of the contact system, and 4) Ruconest – also a C1 inhibitor which is a recombinant product. The first two products are administered subcutaneously and the second two require intravenous access. The importance of having an effective product available and a treatment plan cannot be over emphasized – nor can the mantra 'treat early'.

Dr. Riedl: The treatment of angioedema attacks in HAE requires a highly individualized plan. So there's no single recipe that is going to work best for every person. Everyone with HAE should have an acute medication available – talking through the treatment options with your personal physician is the first important step. We know from the several large clinical studies that have been done over the years that a single dose of any of the FDA-approved acute medications is generally sufficient to stop the attack in the vast majority of cases (~90%). In rare cases, a repeat dose of medication may be needed, but this is where it's important to carefully consider the surrounding treatment issues. Is there another medication that will work more effectively for a specific person? Was the initial dose given properly and early in the attack so as to expect optimal efficacy? Was sufficient time allowed to judge drug efficacy before giving a second dose? There are rare instances where acute medications may be combined to treat severe attacks, though in my experience this usually isn't required if medication is given early and appropriately. But 'troubleshooting' the acute treatment plan with your personal physician is of critical importance if symptoms aren't relieved as effectively as expected.

Dr. Christiansen: I completely agree with the importance of partnering with your physician to find the plan that works best for your individual circumstance and experience. Such factors as the route of drug delivery, ability to learn self-treatment or preference for a visiting nurse (Kalbitor) may influence selection. The emerging area of pharmacogenomics is an interesting topic – in the future it may serve to 'marry' the right drug to the right person.

Dr. Zuraw: I couldn't agree more with you. It's not only an interesting area, but it's a direction that we will certainly be paying a lot of attention to in the future. Right now, we pick the best on-demand medicine based on vague preferences and intuition. Luckily, most of the medicines work most of the time in most of the patients. But wouldn't it be so much better to be able to say, "we know that this particular medicine is the best one for you"? The attempt to do this has been given a specific name – 'precision medicine'. The information that we'll need to make these precise recommendations will come not only from genomics, but also from many other types of information such as epigenomics, metabolomics, etc. that we hope to gather in the future. Once we can do this, we'll expect the on-demand medicine to work with the first dose, virtually all of the time, in all of our patients.

HAE news from around the globe

USA **www.haea.org**

2015 Patient Summit

The next US HAEA National Patient Summit will be held at the Denver Marriott Tech Center in Denver, Colorado on 9-11 October 2015. The summit is a great opportunity to meet new and old HAE friends at a fun and supportive gathering of patients and families, to learn about the latest in angioedema research and treatments, and to have HAE questions answered by expert HAE physicians/scientists. Also, the summit is a chance to speak to insurance and reimbursement specialists as well as to participate in research that will be published in medical journals.

HAE and PTSD

Dr. Sandra Christiansen and her co-investigators at the US HAEA Angioedema Center at the University of California San Diego have initiated a study to understand the relationship between HAE attacks and trauma, stress, anxiety or depression. Understanding how stress may cause attacks of angioedema could ultimately lead to new insights and therapies to reduce the burden of disease and enhance the quality of life of individuals with HAE and their families. This study is a first step in this direction, and seeks to understand the relationships between HAE and stress.

Spain **www.angioedema-aedaf.org**

Of course AEDAF will be devoting a lot of time and effort in the year to come to helping with the organization of the 3rd HAE Global Conference to be held in May 2016 in Madrid and planning something exciting for **hae day :-)** a few days before the conference.

HAE-IN-MOTION

HAEA is hosting its first ever 5K run/walk to benefit HAE patients immediately following the 2015 National Patient Summit in Denver, Colorado. The HAE IN-MOTION 5K is projected to serve as the largest HAE sponsored, national fundraising event. Following the first HAE IN-MOTION 5K, HAEA encourage patients and members of the HAEA community to host their own HAE IN-MOTION 5K events throughout the country to raise awareness and help HAE patients achieve lifelong health.

The name HAE IN-MOTION is chosen to portray the three fundamental pillars of HAEA's overall commitment to improving the lives of HAE patients: (1) The increasing momentum in the research efforts, (2) the mile markers crossed in realizing treatments to help HAE patients lead normal lives, and (3) the strides toward finding a cure. Registration for the event in Denver at www.5k.haea.org.

Canada **www.haecanada.org**

Membership Kits

The HAE Canada membership kits will finally be making their way to the members' homes. The contents of the kit will be useful for current as well as for new members. This has been a huge undertaking for the organization and HAE Canada is happy to have them ready to go.

MedicAlert Foundation Canada Partnership and Membership Offer

Earlier in the year HAE Canada reported that the organization had secured a partnership with the MedicAlert Foundation Canada. HAE Canada is pleased to have partnered with Medic Alert to provide the members with a special membership offer. Information about this special offer will be included in the membership kits. MedicAlert is a trusted registered charity that has protected more than one million Canadians for the past 50 years. HAE Canada is very excited about this partnership and look forward to working with MedicAlert Foundation Canada for many years to come.

Upcoming Patient Events

Planning is well underway for the upcoming patient event in Calgary, Alberta 17 October 2015. Dr. Tom Bowen is confirmed as one of the physician speakers for this event that will be undertaken in partnership with NRBDO Alberta. HAE Canada will be posting additional details about this event on www.haecanada.org over the coming months. Events are also being planned for Winnipeg and Victoria in 2016.

HAE Canada Website

Over the next few months you will see changes to the HAE Canada website that will enable those viewing it on mobile devices to have a better experience. In the latter half of 2015 the member only forum will be launched, which will enable the members to discuss topics of their choice in a secure, password protected environment. Over the coming months resources and information on the website will be updated as well.

HAE Canada Resource List

In the Fall 2015 HAE Canada will be making additional resources available to the members. Along with its partners the organization has been working to develop a list of resources that can be made available to all of the members. HAE Canada will be providing the members with more information about this initiative in the coming months.

Denmark, Norway and Sweden **www.haescan.org**

Patient conference

The first Scandinavian HAE conference will take place on 6-8 November 2015. The venue will be in Nyborg, Denmark.

New website

Furthermore HAE Scandinavia has just launched a new, very intuitive and scalable website that can be approached from any device. The new website hosts a wealth of information, including videos on HAE and material in Danish, Swedish and Norwegian for download. Visit the new page at: www.haescan.org.

Poland **www.hae.org.pl**

HAE Poland will be holding its next national patient meeting in Warsaw 3-4 October 2015.

Continues on next page

United Kingdom **www.haeuk.org**

Changes to the organization

Way back in 2010 HAEi supported patients in the United Kingdom to start HAE UK. At that time the organization faced many challenges: Many patients waited 20 or more years with misdiagnosis and inappropriate treatments and surgeries. Treatment varied from hospital to hospital and there were huge inequalities in access to acute attack medications.

Over the first five years HAE UK has achieved some of the key objectives. The membership is over 350 now. In 2013 the organization achieved an official NHS England Policy for HAE, which means that every HAE patient is entitled to key services, which are paid for centrally by the NHS. This is the single most important thing that has happened for HAE UK, and it is the foundation on which the organization can build and expand its services. HAE UK now has its 2014 Revised Consensus Guidelines, which will develop the HAE management in the future.

The other special thing HAE UK has done over these last years is to develop the organization as a really supportive 'family' who are there for each other through the ups and downs of dealing with our condition.

By now HAE UK is at a stage of change. The needs of the members are too great to be met by the present organizational structure. With this in mind HAE UK became a Charity in 2013, and now the Trustees are working to devise a structure that will meet the challenges of the future. Ann Price will now be stepping down from her voluntary lead role with HAE UK, and the organization will be employing Laura Szutowicz as the new CEO to take HAE UK forward. She will lead all areas of HAE UK activities and will represent HAE UK with all stakeholders. Rachel Annals will continue in her part time executive role supporting Laura Szutowicz as the events organizer and administrator and Furkhanda Haxton will continue in her voluntary role partnering Rachel Annals in managing the HAE UK Facebook group.

Ann Price writes: It has been a great privilege for me to work with Rachel over the past five years to build our HAE UK support organization. It's been wonderful to be part of our global HAE family and to share experiences and friendships with so many lovely people. Thank you for great times together and for all that we have achieved. Now it is time for me to step down from my role, and it's my great pleasure to introduce you to Laura Szutowicz who will be our new UK CEO. I've asked Laura to say a few words about herself, and I know she is looking forward to meeting many of you in person at the HAEi Global Conference next May.

Laura Szutowicz writes: I am very excited and privileged to take over from Ann as CEO of HAE UK. I have spent the past 20 years working in pharmaceutical companies and will be able to bring that business experience into this new role. Much of my time has been spent in Immunology and haemophilia so I do feel I am coming home. Ann has left very large boots to fill (metaphorically!) and I will be trying my hardest to carry on the great legacy she and John have created. My future looks as though it is going to be very busy!

Patient day

Laura Szutowicz will be leading the patient day 7 November 2015 in Birmingham. The theme is 'HAE through all the changing stages of life'. The speakers will include Dr Aarn Huissoon, Consultant Immunologist at Birmingham Heartlands Hospital and Dr Scott Hackett, Consultant Paediatrician at Birmingham Children's Hospital. This is an opportunity to learn from the HAE Experts and to meet up with many friends who know what it is like to live with this rare condition.

Fundraising

During the first five years HAE UK depended solely on the generous sponsorship of the pharmaceutical companies CSL Behring and Shire Pharmaceuticals. Both these companies continue to be very generous in their sponsorship – but the organization do now need to ask the members to consider fund raising – if they are well enough, and are able to help HAE UK in this way. HAE UK will be putting information about fundraising on the website soon with lots of stories from past fundraisers and information on how to support HAE UK. Advice, ideas and a fundraising leaflet can also be obtained by e-mailing:

rachel.annals@haeuk.org.

Let us know what happens in your country

Please send all relevant information about activities in your country to our Communications Manager Mr. Steen Bjerre at s.bjerre@haei.org

Interesting research on normal C1-INH HAE

The Journal of Clinical Investigation has recently published an interesting study entitled "Defective glycosylation of coagulation factor XII underlies hereditary angioedema type III".

This study provides the first scientific evidence pointing to the biological mechanism that causes swelling in patients who have

(1) recurrent swelling attacks,

(2) normal C1 inhibitor, and

(3) a confirmed mutation in the plasma protein Factor XII.

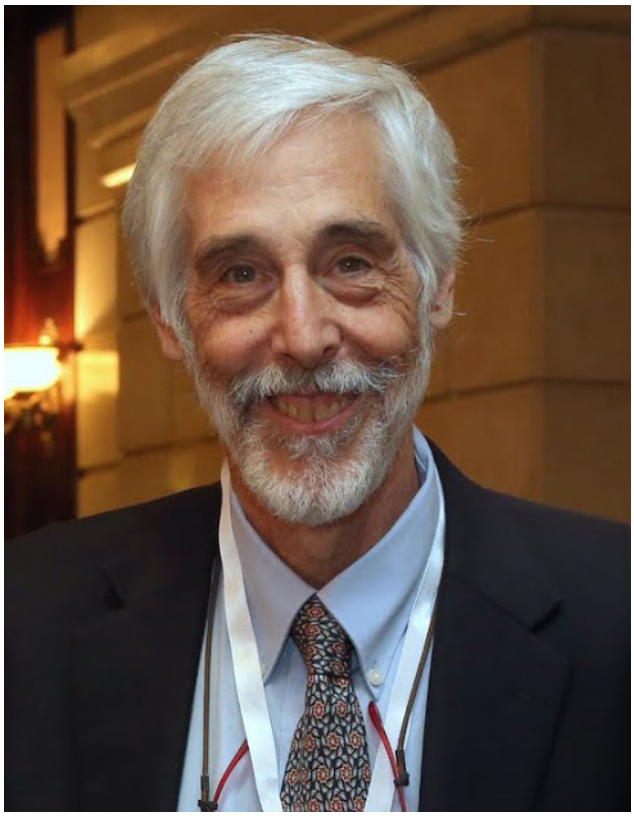
Although an international consensus of scientists recommended using the term "HAE with Normal C1 inhibitor" for patients who fit the three criteria listed above, some scientists and physicians (including the authors of this study) continue to use "HAE III".

The study showed that the biological pathway that leads to swelling in "normal" C1 inhibitor patients with Factor XII gene mutations are caused by the same biological pathway associated with attacks in HAE patients with C1 inhibitor deficiency.

The authors note that their experiments using mice and human blood samples indicate that the current therapies used for HAE types 1 and 2 (namely, plasma derived C1 inhibitors Cinryze and Berinert; the recombinant C1 inhibitor Ruconest; the kallikrein inhibitor Kalbitor; and the B2 bradykinin antagonist Firazyr) have an effect on the biological process that causes swelling attacks due to Factor XII mutations. The scientists draw the same conclusion for two fully humanized antibodies – one designed to act against activated Factor XII, and the other against plasma kallikrein (Dyax's DX-2930 in clinical development for HAE 1 and 2).

We must keep in mind that the testing cited above was done in the laboratory on mice and human blood. Nevertheless, this study appears to be an important scientific step towards understanding, and more importantly, finding effective treatment for HAE patients whose swelling attacks are caused by a Factor XII mutation.

The US HAEA is taking a central role in promoting research into HAE with normal C1INH. HAEi's largest member organization will host the Second International Scientific Conference on HAE with Normal C1 inhibitor. Scientists from around the world will gather to discuss findings of this most recently published paper and other related research projects including one that has just been started at the US HAEA Angioedema Center at the University of California at San Diego.



Professor Bruce Zuraw, Director of the US HAEA Angioedema Center

This research paper raised several questions that were answered by Professor Bruce Zuraw, Director of the US HAEA Angioedema Center in San Diego, California:

How can I get tested for a Factor XII mutation?

Ask your doctor to send a blood sample to the National Jewish Complement Laboratory to screen for this mutation. To get this assay done, you will need to sign a consent form because it involves genetic information. At the moment, they are only running the tests for the specific mutation discussed in this paper. We may learn in the future, that we have to look at more regions in the gene.

What is the diagnosis for patients that have recurrent HAE-like swelling episodes, but don't have a FXII mutation?

The US HAEA Angioedema Center at UCSD is currently doing a study to answer this question.

The paper demonstrates that swelling in patients with HAE w/FXII mutation is caused by the same mechanism (kallikrein-bradykinin) that causes swelling in C1INH deficiency. Does that mean that therapies currently available for HAE 1 and II will be effective for angioedema patients diagnosed with a FXII mutation?

In general, the answer is yes. The major unresolved question is whether or not C1INH therapy makes sense in this situation. At a minimum, this article provides additional ammunition to advocate for use of bradykinin acting drugs for HAE-normal-C1INH.

Why does this paper refer to the condition as HAE III when we have recently seen it labeled as HAE with Normal C1INH?

Getting everyone to use the same terminology is difficult, and it is 'users choice' which term is utilized. As indicated above, this paper does not provide information about HAE-normal-C1INH without a factor XII mutation, showing why the more generic designation is preferable.

Global Advocacy Work

Future activities

17 September HAEi will participate in and host a round-table at the Orphan Drug Summit 2015 in ***Copenhagen, Denmark***.

2-4 October HAEi will participate in the annual patient meeting of our Polish member organization. This year the meeting will take place in ***Warsaw, Poland***.

9-11 October HAEi will participate in the US HAEA National Patient Summit 2015 in ***Denver, Colorado, USA***. This summit is expected to attract 6-700 delegates.

20-21 October HAEi is planning on participating in the WHINN (Weak of Health and Innovation) which will take place in ***Odense, Denmark***. The goal is to gather more information about possibilities in healthcare technology and how HAEi can better utilize technology on a global basis.

30 October-1 November The HAEi Executive Committee will meet in ***Frankfurt, Germany***.

6-8 November HAEi will participate in and speak at the first HAE Scandinavian conference taking place in ***Nyborg, Denmark.***

HAE papers

Here are summaries of some of the recently published HAE related scientific papers:

Phase II study results of a replacement therapy for HAE with subcutaneous C1-inhibitor concentrate – by B.L. Zuraw, University of California, USA, et al.:

This open-label, dose-ranging, crossover study (COMPACT Phase II) was conducted in 18 type I or II HAE patients who received two of twice-weekly 1500 IU, 3000 IU or 6000 IU subcutaneous doses of highly concentrated volume-reduced CSL830 for 4 weeks each. Subcutaneous volume-reduced CSL830 was well tolerated and led to a dose-dependent increase in physiologically relevant functional C1-INH plasma levels. A clinical outcome study of subcutaneous CSL830 in HAE patients warrants further investigation. *(Allergy, May 2015)*

Current state of HAE management: A patient survey - by A. Banerji, Harvard Medical School, USA et al.:

HAE management is improving with good access to on-demand and prophylactic treatment options. However, HAE patients still have a significant burden of disease and continued research and educational efforts are needed. *(Allergy Asthma Proc., May 2015)*

Icatibant in Angiotensin Converting Enzyme (ACE) Inhibitor-Associated Angioedema - by J.S. Fok et al., Royal Adelaide Hospital, Australia:

We treated 13 consecutive Emergency Department patients, who had not improved with adrenaline and/or corticosteroids, with icatibant 30 mg subcutaneously for ACE-inhibitor-associated upper respiratory tract angioedema according to an agreed protocol. All patients improved after receiving icatibant, consistent with its bradykinin-receptor blocking mechanism. Icatibant rapidly reversed symptoms, and appeared to avert the need for intubation or expedite extubation. Timely use of icatibant in ACE-inhibitor associated angioedema may avert the need for invasive airway procedures and intensive care unit admission. *(Intern Med J., May 2015)*

Management of acute attacks of HAE: role of ecallantide - by H. Duffey and R. Firszt, University of Utah, USA:

Ecallantide is generally a safe and well-tolerated medication; however, based on reports of anaphylaxis, ecallantide does contain a black box warning. Due to the risk of anaphylaxis, ecallantide cannot be self-administered and must be given by a health care professional. Overall, ecallantide is a safe and effective medication for the treatment of acute attacks of HAE. *(J Blood Med., April 2015)*

Home Therapy with Plasma-Derived C1 Inhibitor: A Strategy to Improve Clinical Outcomes and Costs in HAE - by A. Petraroli et al., University of Naples Federico II, Italy:

Home therapy with pdC1-INH is a feasible strategy for the management of C1-INH-HAE and may result in cost savings. *(Int Arch Allergy Immunol., April 2015)*

C1-inhibitor polymers activate the FXII-dependent kallikrein-kinin system: Implication for a role in HAE - by D.E. Madsen, University of Southern Denmark, et al.:

The C1-inh polymers might play a role in the pathophysiology of HAE, but several diseases are characterized by the presence of serpin polymers. The role of serpin polymers has so far remained elusive, but our results indicate that such polymers can play a role as inflammatory mediators through the FXII-dependent kallikrein-kinin system. *(Biochim Biophys Acta., June 2015)*

Before and after, the impact of available on-demand treatment for HAE - by C.S. Christiansen et al., University of California San Diego, USA:

With the introduction of newer therapies, subjects with the most severe burden of illness improved more than those with milder burdens. However, significant burden of illness remained. The availability of the current treatments has substantially improved the quality of life for HAE patients in the United States, similar to a survey of Danish HAE patients regarding the introduction of home treatment. Nevertheless, our study shows that a substantial burden of illness remains for HAE patients. *(Allergy Asthma Proc. March-April 2015)*

Bradykinin-mediated angioedema: factors associated with admission to an intensive care unit, a multicenter study - by N. Javaud, Hôpitaux de Paris, France, et al.:

Upper airway involvement is an independent risk factor for ICU admission. Corticosteroid use, which is an ineffective treatment, and C1-inhibitor concentrate use are factors for ICU admission. The presence of upper airway involvement should be a warning signal that the attack may be severe. *(Eur J Emerg Med., February 2015)*

Critical appraisal of androgen use in HAE: a systematic review - by M.A. Riedl, University of California, USA:

Androgen therapy may be effective for most patients with HAE; however, potential risks and adverse effects must be carefully considered and discussed with patients when considering options for long-term HAE prophylaxis. *(Ann Allergy Asthma Immunol., April 2015)*

Recombinant human-c1 inhibitor is effective and safe for repeat HAE attacks - by H.H. Li, Institute for Asthma and Allergy, Chevy Chase, USA, et al.:

A single 50-IU/kg dose recombinant human C1INH was effective for improving symptoms of an HAE attack with sustained efficacy for treatment of subsequent attacks. Recombinant human C1INH had a positive safety profile throughout the study. This study supports repeated use of recombinant human C1INH over time in patients with HAE attacks. *(J Allergy Clin Immunol Pract., May-June 2015)*

HAE and lupus: A French retrospective study and literature review - by I. Gallais Sérézal, Karolinska Institute, Sweden, et al.:

The association between lupus and HAE is a rare but not unanticipated event. Patients are often symptomatic for HAE before developing lupus. Lupus cases associated with HAE share some characteristics of lupus cases related to other complement deficiencies, such as the absence of severity and the predominance of cutaneous symptoms. *(Autoimmun Rev., June 2015)*

Treatment of angiotensin receptor blocker-induced Angioedema: A case series - by U. Strassen et al., Technical University of Munich, Germany:

Icatibant is a safe and effective substance for the treatment of angiotensin II receptor blocker-induced angioedema. Although the pathophysiology of angiotensin II receptor blocker-induced angioedema remains unclear, it appears to be associated with the bradykinin pathway. *(Laryngoscope, February 2015)*

Recombinant human C1 esterase inhibitor for the treatment of HAE due to C1 inhibitor deficiency (C1-INH-HAE) - by G. Sabharwal and T. Craig, Penn State University, USA:

Plasma-derived C1INH has been used to replace the deficiency of C1 inhibitor (C1INH) and has been approved for both treatment of attacks and for prophylactic therapy to prevent attacks. Plasma kallikrein inhibitor (ecallantide) and bradykinin receptor antagonist (icatibant) are both effective for treatment of acute attacks, but their short half-life limits the use for prophylaxis. Androgens, in particular danazol, are effective for long-term prophylaxis, but adverse event profile can limit its use. Recombinant C1 inhibitor derived from transgenic rabbits has recently been approved for use in treatment of C1-INH-HAE attacks and is effective and appears safe with minimal adverse event profile. *(Expert Rev Clin Immunol. March, 2015)*

C1 inhibitor deficiency: 2014 United Kingdom consensus document - by H.J. Longhurst, Barts Health NHS Trust, United Kingdom, et al.:

Here we present an updated 2014 United Kingdom consensus document for the management of C1 inhibitor-deficient patients, representing a joint venture between the UK Primary Immunodeficiency Network and HAE UK. To develop the consensus, we assembled a multi-disciplinary steering group of clinicians, nurses and a patient representative. This steering group first met in 2012, developing 48 recommendations across 11 themes. The statements were distributed to relevant clinicians and a representative group of patients to be scored for agreement on a Likert scale. All 48 statements achieved a high degree of consensus, indicating strong alignment of opinion. The recommendations have evolved significantly since the 2005 document, with particularly notable developments including an improved evidence base to guide dosing and indications for acute treatment, greater emphasis on home therapy for acute attacks and a strong focus on service organization. *(Clin Exp Immunol., June 2015)*

News from the Industry

7 July, 2015

The U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for the investigation of DX-2930 for HAE. Dyax Corp. is developing DX-2930, an investigational fully human monoclonal antibody inhibitor of plasma kallikrein (pKal), as a subcutaneous injection for prevention of HAE attacks.

Breakthrough Therapy designation is intended to expedite the development and review of potential new medicines with early signal of clinical benefit in serious or life-threatening conditions and helps ensure patients have access to them as soon as possible. Breakthrough Therapy designation is considered when preliminary clinical evidence indicates the drug may demonstrate substantial improvement over available therapy. The benefits of Breakthrough Therapy designation include organizational commitment involving the FDA's senior managers and with more intensive guidance. Breakthrough Therapy designation does not change the standards for approval.

The designation is supported by the interim results of Dyax's Phase 1b clinical trial of DX-2930 in HAE patients. The Phase 1b study met all objectives assessing safety, tolerability and pharmacokinetics of multiple subcutaneous administrations of DX-2930. Additionally, in a pre-specified proof-of-concept efficacy analysis, DX-2930 demonstrated statistically significant reductions in attack rate compared to placebo.

"Receipt of Breakthrough Therapy designation is a key milestone for the DX-2930 development program," said Burt Adelman, M.D., Executive Vice President of Research and Development and Chief Medical Officer at Dyax. "We look forward to taking full advantage of the opportunities that Breakthrough Therapy designation allows in order to maximize the possibility of a rapid path to approval."

(Source: Dyax)

21 July, 2015

The global collaboration between Clinigen Group plc and Pharming Group N.V. to provide access to Pharming's Ruconest (conestat alfa) is now live. The unique access program was initiated by HAEi, the International Patient Organization for C1-inhibitor Deficiencies.

Ruconest is a recombinant human C1-inhibitor, approved by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for the treatment of acute attacks of HAE. The "HAEi GAP" program enables patients in all countries where Ruconest is not commercially available to gain access to the drug through an ethical and regulatory compliant "Named Patient Program" mechanism.

Physicians wishing to request Ruconest through the HAEi GAP program should contact the Clinigen customer services team at customer.services@clinigengroup.com or on 0044 1283 494340.

"HAEi is committed to securing access to HAE medications for patients across the globe," said Anthony J. Castaldo, President of HAEi. "We are extremely proud to have established HAEi GAP with our current partners and to be able to announce that, from today, physicians are able to request Ruconest to meet the needs of their patients."

Simon Estcourt, Managing Director, Managed Access, Clinigen Group said: "We are very pleased to work with Pharming to help HAEi realize their mission to ensure that sufferers of hereditary angioedema worldwide can access this effective and potentially life-saving treatment. The ground-breaking program provides Ruconest to patients in an ethical and compliant way, removing the need and the risk for patients to resort to other less reliable or even illegal sources of the drug."

Sijmen de Vries, CEO, Pharming said: "As the first pharmaceutical company to partner with HAEi and provide access to Ruconest through HAEi GAP, we are leading the charge to improve the lives of those HAE patients that otherwise would continue suffering from this debilitating and unpredictable disease."

(Source: Clinigen)

PHARMING

30 July, 2015

From Pharming Group N.V.:

Following the completed acquisition of our **US partner**, Salix Pharmaceuticals by Valeant Pharmaceuticals (VRX), the Ruconest US commercial infrastructure remains intact and commercialisation continues to be unaffected.

A steady inflow of new patients into Ruconest Solutions (the US total care program under which Ruconest is made available to HAE patients in the US) continued during H1 2015.

Patient enrollment for the randomized double blind placebo controlled Phase II clinical trial to investigate Ruconest for the prophylaxis of HAE was initiated in January and continued during the period.

In February, **Dr. Perry Calias** was appointed as Chief Scientific Officer. Dr. Calias has overall responsibility for the Company's new Enzyme Replacement Therapy (ERT) programs, achieving the scientific milestones set in the business plan, enhancing the IP portfolio, overseeing new product development and contributing to the overall strategic direction of the Company.

In May, Pharming and Clinigen Group (CLIN) entered into an international global access collaboration for HAEi, the International Patient Organisation for C1-Inhibitor Deficiencies. The **"HAEi GAP"** program will provide access to Ruconest to eligible patients with HAE, who currently do not have access to effective medication, to treat acute attacks of the disease.

The Company entered into an exclusive distribution agreement with **Cytobioteck S.A.S.** ("Cytobioteck"), a privately owned Bogota, Colombia based specialty healthcare company, for the distribution of Ruconest for the treatment of acute attacks of HAE in Colombia and Venezuela.

(Source: Pharming)

Dyax

12 Aug, 2015

Dyax Corp. has provided an update regarding its ongoing manufacturing initiatives for DX-2930. Discovered by Dyax, DX-2930 is an investigational fully human monoclonal antibody inhibitor of plasma kallikrein being developed for the prevention of HAE attacks.

Dyax's manufacturing partner, Rentschler Biotechnologie GmbH, is responsible for providing cGMP (Current Good Manufacturing Practice) drug substance for certain future clinical trials and commercial supply. In preparation for commercial-scale production, Rentschler has commenced characterization and validation of the DX-2930 manufacturing processes. In addition, Rentschler will also support Dyax in the preparation of its submissions to regulatory authorities for marketing approval of the product. If DX-2930 is approved, Rentschler will be responsible for producing commercial supply. Dyax and Rentschler entered into a definitive manufacturing services agreement in 2014.

"Rentschler is a leading manufacturer of FDA and EMA licensed products, has extensive expertise in high quality production of monoclonal antibodies, and an excellent track record in manufacturing products for both clinical trials and commercial markets," said Gustav Christensen, President and CEO of Dyax. "Their knowledge will be important as we work to prepare the Chemistry, Manufacturing and Controls dossiers and other requisite regulatory filings. We look forward to initiating the Phase 3 trial for DX-2930 in HAE patients during the latter part of this year, and we expect that supportive results from this study will be the basis for our BLA submission to the FDA for marketing authorization."

"We are extremely pleased to be working with Dyax to produce DX-2930," said Dr. Klaus Schoepe, Vice President of Project Management at Rentschler. "We are utilizing our expertise to deliver a first-class quality product and consequently contribute to the availability of this important medicine and the improvement of the health status of patients."

(Source: Dyax)

Continues on next page

News from the Industry

14 Aug, 2015

From ProMetic Life Sciences Inc.:

During the second quarter of 2015, ProMetic selected C1 Esterase Inhibitor ("C1-INH") as its next plasma-derived drug candidate to be developed. The C1-INH protein is most commonly used for the treatment of HAE, a rare genetic disorder in which C1-INH is lacking.

(Source: Prometic)

25 Aug, 2015

Shire plc has announced that it has attained enhanced Cinryze manufacturing flexibility and capacity.

The company has entered into an agreement with Sanquin Blood Supply, the manufacturer of Cinryze® (C1 esterase inhibitor [human]), providing Shire access to its manufacturing technology and allowing Shire to source additional manufacturers to meet the growing demand for Cinryze.

"We wanted the freedom to operate and expand in a way that makes strategic sense for our business," said Flemming Ornskov, M.D., CEO, Shire. "When Shire acquired ViroPharma in January 2014, we inherited an arrangement under which Sanquin was the exclusive manufacturer for Cinryze. We're pleased that Sanquin was open to expanding our partnership and agreeing to support us as we increase production options for this important therapy."

The specific terms of the agreement are confidential, but involve payments to Sanquin on achievement of certain milestones, including a successful technical transfer to a second source manufacturer. Sanquin will continue to serve as a key partner with Shire to increase global supply of Cinryze.

(Source: Shire)

HAEi

HAEi is a global non-profit umbrella organization dedicated to working with its network of national HAE member organizations to raise awareness of HAE.

You are not alone

HAEi around the globe

Currently you will find HAE member organizations in these 46 countries:

Africa: Kenya

Asia: China, India, Japan, Malaysia, Russia, United Arab Emirates

Australia: Australia, New Zealand

Europe: Austria, Belarus, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Macedonia, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, The Netherlands, Ukraine, United Kingdom

North America: Canada, Mexico, United States of America

South America: Argentina, Brazil, Chile, Costa Rica, Ecuador, Peru, Uruguay, Venezuela

You will find much more information on the HAE representations around the globe at www.haei.org. On our World Map you will find contact information for our member organizations as well as care centers, hospitals, physicians, available medication, and clinical trials.

The information on www.haei.org is being updated as soon as we receive fresh data from the national member organization.

Your feedback is very welcome

Please let us know what you believe should be included in future newsletters. You can do that by providing feedback to Executive Director Henrik Balle Boysen or Communications Manager Steen Bjerre. In addition, we invite you to submit articles on any topics that you believe would be of interest to other readers. We look forward to your comments and working with you on future newsletters.

Corporate Information

HAEi is officially registered as a non-profit/ charity organization in the Canton of Vaud in Switzerland. The registered address is:

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