Issue 6 · October 2015

HAEi Newsletter

National Patient Summit in Denver

The US Hereditary Angioedema Association (HAEA) held its National Patient Summit in Denver, Colorado 9-11 October 2015. The weekend was filled with opportunities designed especially for 800 HAE patients, caregivers, family members and others who attended the Summit.

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 6 · October 2015

Front page photo by Sherry Porter from the HAEA National Patient Summit in Denver, Colorado 9-11 October 2015.

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A Message from the President

Dear HAEi Friends,

Welcome to the 6th HAEi newsletter of 2015. We are delighted to provide you with a comprehensive overview of the latest happenings in the global HAE environment.

Here on the east coast of the United States, autumn is well underway with lower temperatures and beautiful landscape views created by the burning colors of fall. I hope that the season in your part of the world brings with it happiness and good health.

Over the years, I have had the good fortune of interacting with and learning from many brave and forward thinking HAE patient advocates who have successfully broadened access to modern medicines in their respective countries. One of these extraordinary leaders described the basis of her success in three simple words—The Power of One. She went on to explain that her steadfast and unwavering motivation initially stemmed from a desire to help her severely affected child. Almost immediately, however, she recognized that other families were also suffering, so she expanded her efforts to include the country's entire HAE population.

At first, this intrepid HAE advocate was a lone voice shouting out to deaf ears in the medical community and health ministry. At that point, the Power of One felt like the Power of None. Nevertheless, she pressed on believing that one person can make a difference and that consistent effort would somehow bring success. And that is exactly what happened. The consistent energy created by the Power of One went viral and the advocacy effort this remarkable advocate started increased exponentially as other HAE patients and key physicians joined in.

My fellow HAEi friends, broadening access to life saving HAE therapies is clearly not an easy task. We do know, however, that it takes just one motivated and persevering person to invoke the Power of One and serve as the force behind a vigorous advocacy movement. Which "One" among us is ready for the challenge?

Warm 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 at the moment:

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

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

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

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 Germany, Mexico, Romania, United Kingdom, and USA.

http://clinicaltrials.gov/show/NCT02052141

A European Post-Authorisation Observational Study Of Patients With HAE

Recruiting in Belgium, France, Germany, Italy, 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

A Phase 2 HAE Prophylaxis Study With Recombinant Human C1 Inhibitor

Recruiting in Canada, Czech Republic, Macedonia, the Netherlands, Romania, and United States.

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

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

Recruiting in Australia, Canada, Czech Republic, Germany, Hungary, Israel, Italy, Romania, Spain, United Kingdom, and United States.

https://clinicaltrials.gov/ct2/show/NCT02316353?term=hereditary+angioedema&rank=11

Screening Protocol for Genetic Diseases of Mast Cell Homeostasis and Activation

Recruiting in United States.

https://clinicaltrials.gov/ct2/show/NCT00852943?term=hereditary+angioedema&rank=62

Pathogenesis of Physical Induced Urticarial Syndromes

Recruiting in United States.

https://clinicaltrials.gov/ct2/show/NCT00887939?term=hereditary+angioedema&rank=63

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

Recruiting in the 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 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.

HAEi 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 the HAEi 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. HAEi therefore advise anyone interested to see their physician to discuss how to best get access to the program. In addition, please feel free to contact HAEi should you have any questions.

HAE GLOBAL CONFERENCE MADRID 19-22 MAY 2016

HAE Global Conference in Madrid

Following the 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. HAEi 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 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 HAEi is 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 the member organizations. HAEi expects to be able to announce more details about the program and the registration process within a month. Announcements of the registration process will take place through this newsletter as well as on Facebook, LinkedIn and Twitter.

Ask the doctors

Earlier this year the US HAE Association implemented a process for answering patients' questions about HAE. 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.

Here is one of the most recent questions – and an extract of the answer from the expert physicians, Dr. Sandra Christiansen, Dr. Marc Riedl, and Dr. Bruce Zuraw.

Why can't Icatibant be used in children? What can happen?

Dr. Christiansen: The limited available pediatric treatment options comprise a serious unmet need. The FDA approved on-demand drugs include: Ecallantide, for ages 12 and older; Icatibant, for ages 18 and older; plasma derived C1 inhibitor and recombinant human C1 inhibitor for adolescents and adults. The reason that we do not have approval for the use of these drugs in children is not an issue of safety or efficacy concerns in younger age groups but rather a reflection of the difficulties drug companies face conducting trials in 'protected populations' such as children and pregnant women. To get their drugs approved and available for use pharmaceutical companies appropriately initially target the 'low hanging fruit', that is the older age groups. We are grateful to have the options for treatment that are now available. We cannot rest however until these options are approved and thereby easier to obtain for all our patients – including children.'

Dr. Zuraw: HAE is a disease that presents in childhood. Dr. Christiansen and I have been working on a manuscript that highlights the pattern that earlier onset of swelling tends to accompany greater disease severity and longer delays to correct diagnosis. Thus, there is a compelling need to make the diagnosis of HAE at a younger age and have on-demand medicines available to treat children. While not currently approved for use in children, physicians can use medicines 'off label'. I have recommended some of these medicines for children. The biggest hurdle, however, is getting them approved by the insurance companies. The limited data that is available for ecallantide and C1 inhibitor suggests that their safety and efficacy is similar to that seen in adults. There is no published data that I'm aware of regarding the use of icatibant in children, however I know that Shire is currently conducting a trial in children.

Dr. Riedl: Icatibant is not FDA-approved for use in people under the age of 18. This is due to a lack of safety and efficacy data of the medication in this younger population, as children and adolescents were not included in the initial pivotal studies on icatibant for HAE. So currently we just don't have enough information to know how well it works or what side effects might occur in children. Safety is, of course, of utmost importance in kids so we need to carefully examine this in controlled, monitored studies. Currently, specific pediatric studies on HAE medications – including icatibant, ecallantide, C1INH and recombinant C1INH – are ongoing. Hopefully, once completed, these will give us additional data on which HAE drugs can be used safely and effectively in younger age groups.

HAE news from around the globe

New Zealand **www.haeaustralasia.org.au**

People with HAE are the first to benefit from the increased competition for rare disorders medicines promoted by Pharmac, the government agency that decides which pharmaceuticals to publicly fund in New Zealand. Pharmac has approved an agreement with Shire Pharmaceuticals to fund icatibant (Firazyr). Chief Executive Steffan Crausaz says Pharmac began testing a new approach to promote competition in 2014, seeking better access to medicines for people with rare disorders. Pharmac identified up to 25 million NZD (14.1 million EUR) available over five years, and sought proposals from companies supplying medicines for rare disorders. The agency received proposals for 28 medicines, many of them previously not seen in New Zealand before and from suppliers Pharmac has not previously done business with. Shire, for example, had not previously supplied medicines in the country. Pharmac estimates there may be up to 90 patients with HAE in New Zealand, of whom up to 25 may meet the criteria for funded treatment with icatibant.

Germany **www.angiooedem.de**

HAE Germany will be having two activities in November 2015: First the 20th meeting of the German Society for Angioedema (Deutschen Gesellschaft für Angioödeme) taking place in Mainz on 18 November and then on 28 November a three-country-meeting organized in cooperation with Uniklinik München.

Switzerland **www.hae-vereinigung.ch**

The 14th meeting for the members of the Swizz HAE organization will take place on 6 November 2015 in Olten.

Turkey **https://www.facebook.com/groups/hereditoranjiyoodem**

The most recent member to the international HAE family is HAÖ Hasta Yardımlaşma ve Dayanışma Derneği – the Turkish HAE organization located in Karşıyaka/İzmir, Turkey. Gökben Yurdakul is President of the organization and can be contacted at:

gokbenyurdakul@hotmail.com.

You can follow the Turish HAE patients on Facebook at this address: https://www.facebook.com/groups/hereditoranjiyoodem.

For many years there has been a lot of HAE patients in Turkey – with great troubles during diagnosing and treatment. However, in recent years the increase in international research, more well-educated doctors and general improvements has led to changes for the patients. With the help of professors and the government HAE Turkey has been formed in order to increase sharing and helping among HAE patients. Being a newly established organization creates a number of challenges but HAE Turkey is doing its best to help HAE patients all over the country. The organization has establish a traveling school that can tour around Turkey and teach doctors and patients how they deal with HAE. The biggest goal of the organization is to develop an active mind against HAE – and over the coming 10 years with passion to change things in a positive way in Turkey.

Colombia **www.facebook.com/pages/Asociación-Colombiana-de-Angioedema-Hereditario/119669588091359**

One more South American country has been added to the HAEi world map as Colombia has joined the family. The HAE contact in Colombia is Jackeline Sus Moreno who can be contacted at:

jacksus2@hotmail.com.

If you want to take a closer look at the HAE organization in Colombia, please visit the national Facebook group at www.facebook.com/pages/Asociación-Colombiana-de-Angioedema-Hereditario/119669588091359.

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

Recently HAE Scandinavia 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 held its annual meeting in Warsaw, Poland early October 2015. To fulfill his desire to expose patients to treatment philosophies and practices in other countries, HAE Poland's President Michal Rutkowski invited HAEi President Anthony J. Castaldo and HAEi Executive Director Henrik Balle Boysen, Professor Marc Riedl from the US HAEA Angioedema Center at UC San Diego, and Professor Marcus Margerl from Charité Hospital in Berlin, Germany. In remarks during the conference's closing session, Michal Rutkowski challenged Polish HAE patients and their physicians to build off progress made to date by stepping up efforts to increase awareness, diagnosis, and intelligent use of available therapies.

At the Polish conference from left to right: Henrik Balle Boysen (Executive Director, HAEi), Michal Rutkowski (President, HAE in Poland - and Vice President, HAEi) and Anthony J. Castaldo (President HAEi and US HAEA)

Canada www.haecanada.org

Membership

The membership continues to grow and now stands at 310 members, which represents a 52 % increase since 1 July 2014.

Website

Over the summer HAE Canada successfully migrated the website to a new IT provider. As a result, the site is now more easily viewed on all mobile devices. Work is underway to make the site bilingual (English/French). HAE Canada anticipates work being completed on this aspect in late fall.

Resource List

The final touches are being put on the HAE Canada resource list. The organization has been working with its partner organizations to identify additional resources of interest to the members. All resources listed will be available free of charge to HAE Canada members and they will be sent directly to the home of the members – postage paid.

HAE Radio

HAE Canada is proud to announce the latest way to disseminate information to the members called 'HAE Radio'. Over the coming year the organization will produce a total of four podcasts that cover a wide range of topics of interest to the members. To ensure that they are kept abreast of what is happening globally, HAE Canada has partnered with HAEi, who will help the organization provide news from around the globe for each podcast. These audio recordings will eventually be available on the website and on iTunes, Soundcloud and Stitcher. Links to each podcast will also be made available on the HAE Canada Facebook page. Stay tuned for more.

Patient meeting

The next patient event took place in Calgary, Alberta 17 October 2015. Dr. Tom Bowen was one of the physician speakers for this event that was undertaken in partnership with NRBDO Alberta. Events are also being planned for Winnipeg and Victoria in 2016.

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USA **www.haea.org**

2015 Patient Summit

Over 800 patients, caregivers, and others attended the US Hereditary Angioedema Association's (HAEA) 2015 National Patient Summit in Denver, Colorado October 9-11 2015. The summit began on Friday night with a welcome reception and concluded on Saturday night with dinner and entertainment that included some wonderful hours of music and fun.

The weekend was filled with opportunities designed especially for HAE patients, caregivers and families. HAEA friends gathered in a fun environment to learn about the latest information on HAE research and treatments. Attendees also had plenty of time to interact with fellow patients, the nation's top HAE physician/scientists, and companies who manufacture and distribute HAE therapies. The summit featured completely new HAE content, up-to-date information, and inventive ways HAEA members could join in 'Shaping the Future Together'.

An amazing 800 people were gathered at the 2015 US HAEA Patient Summit in Denver. The top picture shows a youth panel discussing HAE topics - as part of The Year of the Youth.

Attendees contributed to medical science and furthering the understanding of HAE with on-site research opportunities. Current public policy work in Washington DC was reviewed and information was presented on how HAE patients in the US can influence legislation that affects HAE patients and families.

Patient Services Team members greeted friends new and old, offered help with some new HAEA resources and helped the teens in their Teen Program to scout out Scavenger Hunt prizes. The youngest of the summit attendees met in the Kids Program and provided a sing along about Shaping the Future Together that brought down the house.

It is difficult to sum up all three days of the summit – so many opportunities for all who came to the Colorado Rockies – but in brief, it brought the patient community closer and inspired the participants to continue to Shape the Future Together.

HAE-IN-MOTION

Adding to the excitement of the patient summit, the US HAEA held its first time ever 5k Run/Walk "HAE IN-MOTION" to benefit the HAEA Scholarship Fund. Nearly 250 people ran or walked the race route or cheered from the sidelines. Awards presented were provided to some local professional runners as well as patients and family.

From the US HAEA Angioedema Center

This summer Dr. Riedl also participated in a series of HAE lectures for the Pri-Med Medical Conferences, a continuing medical education program for primary care physicians held at sites across the country. Each regional conference draws 500-700 physicians from a variety of specialties so it was an excellent venue for education on HAE. It was exciting to see signi cant interest from the attendees and lots of questions about HAE. The US HAEA Angioedema Center will keep spreading the word in an effort to improve HAE recognition and clinical care.

Large picture: Leigh Castaldo Farrar and Sherry Porter (US HAEA).
Smaller pictures left to right: HAE Youngsters celebrating 5K run, US HAEA Patient Services Team with HAE In Motion shirts, 5K run medals.

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United Kingdom **www.haeuk.org**

Changes at HAE UK – part 2

Way back in 2010 HAEi supported patients in the United Kingdom to start the national patient group HAE UK. The founder of the Charity and first CEO was Ann Price who has stepped down now as CEO although is remaining as a Trustee. In the past five years Ann has achieved a tremendous amount with a current HAE UK membership of 350. She has also been instrumental in changing policy in the National Health Service (NHS) to ensure better treatment for UK patients, although there still are some changes to make. The other special thing Ann has done over these last years is to develop HAE UK as a really supportive 'family' who are there for each other through the ups and downs of dealing with HAE.

Laura Szutowicz says she has 'quite an act to follow' and her first three months as CEO have been packed with training, getting to grips with the NHS policies and meeting the various key clinicians and people she will need to work closely with over the next months and years to ensure HAE UK can continually move forward. Next year will see a revision/update of the NHS England Policy and with ever more data coming out from the various clinical trials in HAE the UK organization will hopefully be able to broaden the scope of the Policy document to reflect these advances.

Patient Day

The next big event in the UK is the annual Patient Day 7 November 2015. It moves around the country so as to be available to as many patients as possible and this year it is in Birmingham. The team at Heartlands Hospital, headed by Dr. Huissoon and Dr. Hackett, are providing the clinical input to the theme of 'HAE though the lifespan'. There will be presentations on diagnosis and treatment in childhood, dealing with HAE in pregnancy and the challenges faced in the older patient with HAE. This amongst other topics and the ever-popular patient stories, breakout discussion groups and then a panel discussion will make for a busy day.

Australia **www.haeaustralasia.org.au**

Meet Up in Brisbane

17 October 2015 it was time to have a meetup for the patients in and around the Brisbane area – another great opportunity to get together to have a chat over lunch.

Meet Up in Western Australia

29 November 2015 Western Australia HAE patients and carers are invited to attend a Meet Up in East Fremantle. This is an opportunity to meet with others affected by HAE, share stories and hear and learn more about HAE. The guest speakers are A/Prof Richard Loh (HAE in pregnancy and children), Health & Wellbeing Coach Kathy Stratford (stress management and meditation techniques), and Dr. Dominic Mallon (general information on HAE). Morning tea, lunch and afternoon tea will be provided free of charge.

Quality of Life Survey Results

At the annual meeting in Sydney in May, 22 patients participated in a HAE Australasia Patient Survey run by Professor Katelaris. The survey found that nearly half of those surveyed were diagnosed because of an affected family member; one "lucky" person was diganosed correctly after their very first angioedema attack and 11 people waited many years for a correct diagnosis.

Half the survey group stated they experienced one attack per month on average, while six people experienced more than one attack a fortnight and one person averaged two attacks per week. In the last 12 months, most people had missed days from work as a direct consequence of HAE; seven respondents had lost five days and only one had not missed work because of HAE.

The advent of self management and the availability of "on demand" treatment has definitely impacted positively on the lives and well being of those living with HAE and this is reflected in the marked reduction in the number of visits needed to the emergency department in the last 12 months.

Those living with HAE continue to nominate "stress" as the single most common cause precipitating an attack (15/22); trauma was nominated by 14; infection by eight and menstrual period a trigger in five people.

The survey explored members' use of HAE medication. Both tranexamic acid (50 %) and danazol (75 %) had been used by many respondents. Not surprisingly in this adult population, most had found danazol more effective than tranexamic acid. Firazyr (icatibant) had been used by 15 of 19 who replied to this question; one person had not found it effective and one was unsure regarding its effectiveness but all others had found it effective.

This survey, as did the previous one of Australians living with HAE, has shed light on the continuing burden of having this disorder and while the situation has definitely improved, there is still more to be done.

HAE Australasia thank all those who took the time to participate in the survey. It is only by knowing about the burden faced by those with HAE and their continuing difficulties that it is possible to advocate for improvements in management.

Peru www.facebook.com/ AngioedemaHereditarioPeru

From Dr. Oscar Calderon Llosa in Peru the HAEi newsletter has received this information:

My name is Oscar Calderon LLosa MD, allergist specialized in Hospital Universitario la Paz, Madrid, Spain from 2009-2013. Nowadays I'm working in my country, Peru. Peru – located in South America near to the Pacific Ocean – is also known as "The Inca's land". Here like in other countries of this continent the term HAE is practically unknown in the general population.

I would like to tell you about a HAE case that I know of. Suzet Lam Torres, who is the contact person of the Peruvian HAE organization, is an HAE patient and her family as well is diagnosed with HAE. Suzet is a 53 years old Peruvian woman diagnosed in the Red Cross (Holland) in 1993. The laboratory findings were: C1 sterase inhibitor antigen concentration < 0.15 g/l (0.21-0.36), C1 sterase inhibitor activity <0.05 U/ml (076–1.33), C4: 41 mg/l (140-343).

The clinical findings in Suzet are important:

1) Peripherial angioedema and abdominal pain, with repercussion in her lifework (laboral absence) and social activities,
2) Corticosteroids and antihistamines were administered without improvement before the diagnosis. During acute attacks she has taken many drugs without good results, currently when she has attacks she only takes symptomatics like hyoscine for the abdominal pain, waiting for a spontaneous improvement.

Suzet's family has similar laboratory findings with decreased values of C1 sterase inhibitor antigen concentration, C1 sterase inhibitor activity and C4.

The acute attacks are frequent in this family (each 2-3 months), two of them take Danazol 200 mg three times in a week regularly. Suzet's niece suffered a seizure episode while she was working (stress trigger) without angioaedema, the magnetic resonance was normal, no metabolic alteration according to the laboratory findings in that moment, so I ask myself 'Could it be HAE?'

The peruvian HAE organization knows four families diagnosed with HAE and maybe more families are undiagnosed in Perú. We don't know that exactly, but we do know the importance of the treatments like Berinert, Cinryze, Firazyr, and Ruconest in HAE disease. This is a limitation in countries in South America where these drugs are unknown and the use of alternative treatments like androgens and tranexamic acid has bad/regular response in the acute attacks.

For these reasons, HAEi plays an important role in providing advice and performing prevention programs, accurate diagnosis, and specific treatments for the patients with HAE disease specially in the acute attacks, avoiding fatal episodes.

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

Global Advocacy Work

Recent activities

4-6 August HAEi met with the President of the Philippine Society for Orphan Disorders (PSOD) and the Chairman of the organization's Medical Advisory Board in ***Manila, Philippines***. PSOD has built an impressive organization over the years with much of its funding coming from Genzyme and government sources. Among many accomplishments, PSOD rallied support to convince the Philippine Department of Health to provide reimbursement for Lysosomal Storage Diseases. The group is looking to duplicate that success with other rare diseases in general and specifically HAE. PSOD is preparing a plan that will include a countrywide HAE awareness campaign, establishing a center for testing C4 levels, and HAE training for Allergy and Immunology specialists.

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

2-4 October HAEi participated in the annual patient meeting of our Polish member organization, taking place in ***Warsaw, Poland***.

9-11 October HAEi participated in the US HAEA National Patient Summit 2015 in ***Denver, Colorado, USA***.

22-23 October HAEi participated in meetings with Clinigen in ***Burton-on-Trent, United Kingdom*** to further enhance the focus on the HAEi Global Access Program.

Future activities

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

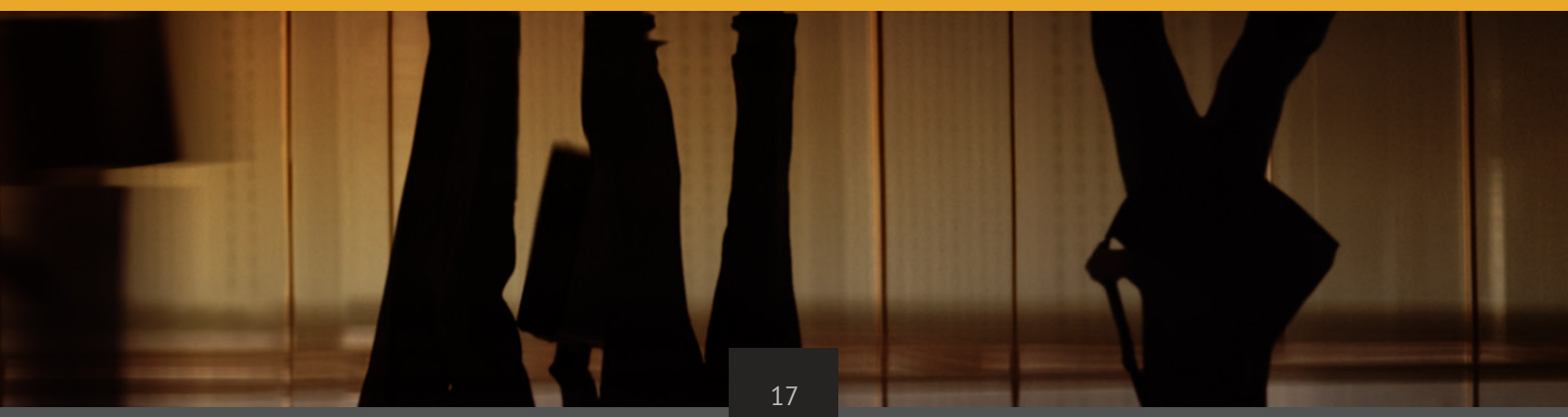
6-8 November HAEi will participate in and speak at the first HAE Scandinavian conference taking place in ***Nyborg, Denmark***.

13-15 November HAEi will participate in and speak at the 2015 Shire Global HAE Forum in ***Madrid, Spain***.

27-30 November HAEi is currently planning an HAE educational meeting for physicians, nurses, and patients in ***Iceland***. During the meeting, we will work with local patients who have expressed interest in becoming a member of HAEi.

11-13 December HAEi is planning on participating in the Middle East Asthma, Allergy and Clinical Immunology Conference in ***Abu Dhabi, United Arab Emirates***.

14-15 January HAEi will participate in the Plasma User Group (PLUS) Consensus Meeting in ***Estoril, Portugal***.



HAE papers

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

Deficiency of plasminogen activator inhibitor 2 in plasma of patients with hereditary angioedema with normal C1 inhibitor levels – by K. Joseph, Medical University of South Carolina, USA, et al:

HAE with normal C1 inhibitor levels (HAE-N) is associated with a Factor XII mutation in 30 % of subjects; however, the role of this mutation in the pathogenesis of angioedema is unclear. We sought evidence of abnormalities in the pathways of bradykinin formation and bradykinin degradation in the plasma of patients with HAE-N both with and without the mutation. Bradykinin degradation was normal in all but 1 of 23 patients with HAE-N studied. By contrast, there was a marked abnormality in PAI-2 levels in patients with HAE-N that is not seen in patients with C1 inhibitor deficiency. PAI-1 levels varied considerably, but a statistically significant difference was not seen. A link between excessive fibrinolysis and bradykinin generation that is estrogen dependent is suggested. *(J Allergy Clin Immunol., September 2015)*

Urticaria and Prodromal Symptoms Including Erythema Marginatum in Danish Patients with HAE – by E.R. Rasmussen et al., Koege-Slagelse Hospital, Denmark:

Erythema marginatum is a characteristic skin rash seen in patients with HAE; however, it can be confused with urticaria, leading to delay in correct diagnosis. 56 % of 87 patients had a positive history of erythema marginatum. Half of the patients had experienced erythema marginatum being misinterpreted as urticaria. The most prevalent other prodromal symptoms were other skin symptoms, malaise, psychological changes, fatigue and gastrointestinal symptoms. HAE patients with erythema marginatum have a longer diagnostic delay, presumably caused by misinterpretation of the rash as urticaria. *(Acta Derm Venereol., September 2015)*

Analysis of characteristics associated with reinjection of icatibant: Results from the icatibant outcome survey – by H.J. Longhurst et al., Barts Health NHS Trust, London, United Kingdom:

Phase 3 icatibant trials showed that most HAE acute attacks were treated successfully with one injection of icatibant. We conducted a post hoc analysis of icatibant reinjection for HAE type I and II attacks in a real-world setting by using data from the Icatibant Outcome Survey, an ongoing observational study that monitors the safety and effectiveness of icatibant treatment. Most HAE attacks resolved with one icatibant injection. There was no distinct profile for patients or attacks that required reinjection when outliers with substantially different patterns of use were excluded. *(Allergy Asthma Proc., September 2015)*

Efficacy of on demand treatment in reducing morbidity in patients with HAE due to C1 inhibitor deficiency – by A. Zanichelli et al., Università degli Studi di Milano, Italy:

On demand treatment is effective in reducing disease related morbidity. The use of on demand treatment in Italy has increased up to 50 % of attacks in the last years reflecting a better adherence to international guidelines. *(Allergy, August 2015)*

Defective glycosylation of coagulation factor XII underlies HAE type III – by J. Björkqvist et al., Karolinska Institutet, Stockholm, Sweden:

The results of this study characterize the mechanism of HAEIII and establish plasma protease factor XII (FXII) inhibition as a potential therapeutic strategy to interfere with excessive vascular leakage in HAEIII and potentially alleviate edema due to other causes. *(J Clin Invest., August 2015)*

Safety and efficacy of C1 esterase inhibitor for acute attacks in children with HAE – by W. Lumry, AARA Research Center, Dallas, Texas, USA, et al.:

Human plasma-derived nanofiltered C1 esterase inhibitor (C1 INH-nf) is used to treat acute angioedema attacks in patients with HAE, but data regarding use in children are sparse. Patients 2 to <12 years of age with a diagnosis of HAE type I or II were recruited for a multicenter open-label trial. Nine children were treated. Treatment of a single angioedema attack with C1 INH-nf doses of 500 U (in patients 10-25 kg), 1000 U, and 1500 U (in patients >25 kg) were well tolerated. Doses of C1 INH-nf <1000 U may be appropriate in some pediatric patients. *(Pediatr Allergy Immunol., July 2015)*

Type I and Type II HAE: Clinical and Laboratory Findings in Iranian Patients – by F. Kargarsharif, Tehran University of Medical Sciences, Iran, et al.:

The patients with a history or symptoms of angioedema who were referred to Immunology, Asthma and Allergy Research Institute (IAARI) 2006 to 2014, were assessed based on a specific questionnaire and laboratory evaluation. The patients with a definite diagnosis of HAE type I and type II were entered into the study. Among 51 patients, 63.3 % were diagnosed with HAE type I and 36.7 % with HAE type II. 15 patients were under 18 years and 36 were adults. The mean age of symptoms onset and diagnosis were 12.33 ± 10.20 years and 24.48 ± 14.64 years, respectively. The mean delay of diagnosis was 11.02 ± 11.60 years. The most commonly involved locations of edema were hands, face and genitalia. Laryngeal edema was observed in 61.2 % of patients, which led to death in two patients during this study. The outcomes of the study can be used to inform clinicians and health care providers about HAE, which can help earlier diagnosis and better management of the patients, specifically in life threatening attacks. *(Arch Iran Med., July 2015)*

A Nationwide Study of Norwegian Patients with HAE with C1 Inhibitor Deficiency Identified Six Novel Mutations in SERPING1 – by I. Johnsrud, Oslo University Hospital, Norway, et al.:

As SERPING1 mutations in Norwegian patients with C1-INH-HAE are largely undescribed and could help in diagnosis, we aimed to find and describe these mutations. 52 patients from 25 families were included. 44 (84.6 %) suffered from C1-INH-HAE type I and eight (15.4 %) suffered from C1-INH-HAE type II. Pathogenic or likely pathogenic mutations were found in 22/25 families (88 %). 13 unique mutations were detected, including six previously undescribed. *(PLoS One., July 2015)*

Development and content validity testing of a patient-reported outcomes questionnaire for the assessment of HAE in observational studies – by M. Bonner, Adelphi Values, United Kingdom et al.:

Patient and expert input has contributed to the development of a content valid questionnaire that assesses concepts important to HAE patients globally. HAE patients across cultures consider the patient reported outcome (PRO) tool a relevant and appropriate assessment of HAE attacks and treatment. *(Health Qual Life Outcomes, July 2015)*

Plasma-derived C1-INH for managing HAE in pediatric patients: A systematic review – by T.J. Craig, Penn State University, USA, et al.:

Available data indicate that plasma derived C1-inhibitor is a safe, effective treatment option for HAE in pediatric patients, including those below 12 years of age. Other therapies also appear safe for the under 12 year of age, but less data are available. Importantly, home-based treatment of HAE in this age group appears to be safe and effective and can improve quality of life. These findings support current HAE consensus guidelines which strongly recommend the use of plasma derived C1-inhibitor as a first-line treatment in children and encourage home and self-treatment. *(Pediatr Allergy Immunol., September 2015)*

Patients perception of self-administrated medication in the treatment of HAE – by A. Wang, Pennsylvania State University College of Medicine, USA, et al.:

92 patients were contacted and 59 agreed to participate. With 69 % of those patients currently undergoing self-administered treatment, the results showed minimal depression and anxiety, a high satisfaction with treatment, and significant compliance with treatment. Most of those not yet on self-administered therapy wanted to start despite being satisfied with the care received in the emergency department. They also believed care at home would be optimal. The main concern of the two groups was not being able to treat themselves in the event of an HAE attack. *(Ann Allergy Asthma Immunol., August 2015)*

Diagnostic and therapeutic management of HAE due to C1-inhibitor deficiency: the Italian experience – by M. Cancian, Università degli Studi di Padova, Italy, et al.:

In 2012, an Italian network for C1-INH-HAE (ITACA) was established by physicians of 17 HAE reference centers to collect data from Italian patients and to homogenize and improve the diagnostic and therapeutic approach to the disease. There is a widespread agreement on therapeutic goals and treatment of C1-INH-HAE acute attacks, but different approaches to prophylaxis are still present among HAE experts. The clinical experience of ITACA on a large population of C1-INH-HAE patients followed for several years may help in identifying the most effective strategies for the management of the disease. *(Curr Opin Allergy Clin Immunol., August 2015)*

News from the Industry

30
Sept, 2015

BioCryst Pharmaceuticals, Inc. has elected Sanj K. Patel to the Company's Board of Directors. Mr. Patel has a proven track record of successfully developing and commercializing new products for rare diseases, and a deep interest in providing breakthrough treatments for these patients. He has leveraged his broad experience base in R&D, marketing and sales to grow and build companies that benefit patients and generate extraordinary value for all stakeholders.

Sanj Patel formed Synageva in 2008 and was its President & CEO through the company's 8.4 billion USD acquisition by Alexion Pharmaceuticals in 2015.

"In recent years, I have gotten to know the BioCryst team, and we share a passion for developing and commercializing novel treatments for rare diseases. With results from two clinical trials for the prevention of hereditary angioedema attacks expected in 2015, it is an exciting time to join the BioCryst Board of Directors," said Mr. Sanj Patel. "I look forward to working with the Board and the BioCryst Leadership Team as the Company advances toward commercialization of oral treatments for rare disease."

(Source: BioCryst)

1
Oct, 2015

The European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP) has adopted a positive opinion recommending DX-2930 for designation as an orphan medicinal product for the treatment of HAE. Dyax is developing DX-2930, an investigational fully human monoclonal antibody inhibitor of plasma kallikrein (pKal), as a subcutaneous injection for prevention of HAE attacks.

"There is a significant unmet medical need for a prophylactic treatment option for HAE," said Burt Adelman, M.D., Executive Vice President of Research and Development and Chief Medical Officer at Dyax. "Our regulatory strategy supports our global development plan for DX-2930 and our goal for providing an improved therapy for patients with HAE around the world. We look forward to initiating a Phase 3 clinical trial for DX-2930 for HAE prophylaxis by year-end 2015."

Under the EMA guidelines, the COMP adopts an opinion on the granting of orphan drug designation, after which the opinion is submitted to the European Commission (EC) for the endorsement of the opinion. Orphan drug designation by the EC provides regulatory and financial incentives for companies to develop and market therapies that treat a life-threatening or chronically debilitating condition affecting no more than five in 10,000 persons in the EU, and where no satisfactory treatment exists, or where a treatment exists, a new treatment may provide a significant benefit to patients affected by the condition. Additionally, this designation provides up to 10 years of market exclusivity if the product candidate is approved for marketing in the European Union and the orphan designation is maintained. Orphan status also permits EMA assistance in optimizing the candidate's clinical development through participation in clinical trial design and preparation of the product marketing application. Orphan Medicinal Product designation does not change the standards for approval.

DX-2930 has previously been granted Orphan Drug, Fast Track and Breakthrough Therapy designations from the U.S. Food and Drug Administration (FDA) for the prevention of attacks of HAE.

(Source: Dyax)

PHARMING

8 Oct, 2015

The U.S. Food and Drug Administration (FDA) has granted 12 years of exclusivity to Ruconest® (C1 esterase inhibitor [recombinant]) 50 IU/kg. The determination of exclusivity ensures that FDA will not approve before July 16, 2026 any applications for biosimilars of Ruconest— i.e. applications for recombinant C1 esterase inhibitors referencing Ruconest submitted under section 351(k) of the Public Health Service Act under the framework established by the Biologics Price Competition and Innovation Act of 2009.

Ruconest was approved by the FDA on July 16, 2014, for the treatment of acute angioedema attacks in adult and adolescent patients with HAE. Effectiveness was not established in HAE patients with laryngeal attacks.

Under the Biologics Price Competition and Innovation Act of 2009, exclusivity for licensed biologics— like Ruconest— can be granted for a 12-year period from the date of first licensure of the product.

"We are pleased the anticipated exclusivity for Ruconest has been formally granted," said Deb Jorn, Executive Vice President/Company Group Chairman, Valeant Pharmaceuticals. "The response to Ruconest has been positive since its launch in November 2014 and we look forward to continued growth."

Sijmen de Vries, the CEO of Pharming Group NV, commented: "Pharming strived to make Ruconest available to the HAE patient community in the US, because we were aware of the great value

and benefits that Ruconest could provide to patients. That the FDA granted 12 year exclusivity for Ruconest reinforces this long-standing commitment and we are excited to continue to work closely with Salix to ensure patients in the US have access to Ruconest."

While Pharming Group NV is developing innovative products for the treatment of unmet medical needs, Salix Pharmaceuticals, a division of Valeant Pharmaceuticals International, Inc., develops and markets prescription pharmaceutical products and medical devices for the prevention and treatment of gastrointestinal diseases.

(Source: Pharming)

BioCryst Pharmaceuticals, Inc.

8 Oct, 2015

BioCryst Pharmaceuticals, Inc. has completed enrollment in OPuS-2 (Oral ProphylaxiS-2), a blinded, randomized, placebo-controlled clinical trial of orally-administered avoralstat in patients with HAE.

OPuS-2 is a 12-week, three-arm, parallel cohort trial designed to evaluate the efficacy and safety of two doses of avoralstat, 300 mg and 500 mg, administered three-times daily compared with placebo. This trial is being conducted in the U.S., Canada and Europe. The primary efficacy endpoint for the trial is the mean angioedema attack rate, which will be reported for each avoralstat dose group compared to placebo.

Final patient visits will occur in January 2016; therefore, BioCryst expects to report OPuS-2 results in early 2016. The results of this trial will be provided for regulatory discussions intended to determine the scope of any additional information that may be required for completion of avoralstat registration.

BioCryst has been corresponding with regulatory agencies regarding deferral of a two-year rat carcinogenicity study for avoralstat. The results from this type of study are normally required to be available at the time of submission for approval. Currently, BioCryst has agreement with the European Medicines Agency (EMA) regarding its request to defer submission of results as a post-filing commitment. Agreement has not been reached with the U.S. Food and Drug Administration (FDA) regarding a deferral at this time. At the end-of-Phase 2 meeting following the completion of OPuS-2, BioCryst will engage in further dialogue with the FDA to discuss deferral, in the context of all available toxicology and clinical data. BioCryst plan to initiate a rat carcinogenicity study in early 2016. Without a deferral, the NDA filing would occur in 2018.

Discovered by BioCryst, avoralstat is a novel, selective inhibitor of plasma kallikrein in development for prevention of attacks in patients with HAE. By inhibiting plasma kallikrein, avoralstat suppresses bradykinin production. Bradykinin is the mediator of acute swelling attacks in HAE patients.

(Source: BioCryst)

Continues on next page

News from the Industry

8 Oct, 2015

BioCryst Pharmaceuticals, Inc. has announced that the randomized, placebo-controlled, Phase 1 clinical trial of orally-administered BCX7353 in healthy volunteers successfully met all of its objectives. The safety, tolerability, drug exposure and on-target plasma kallikrein inhibition results strongly support advancing the development program into a Phase 2 study in HAE patients.

Oral BCX7353 was generally safe and well tolerated at all doses up to 500 mg once-daily for 7 days and 350 mg once-daily for 14 days in healthy volunteers, and no dose-limiting toxicity was identified. There were no serious adverse events (AEs) and most AEs were mild. Two subjects discontinued the study due to moderate gastrointestinal AEs. One subject developed a delayed-type hypersensitivity rash after completing seven days of study drug; the rash resolved quickly with oral and topical steroids. No clinically significant laboratory abnormalities were seen at any dose or duration tested.

BCX7353 plasma levels increased in approximate proportion to dose, and drug exposure was not affected by dosing with food. The half-life of BCX7353 was estimated at 50-60 hours. After daily dosing, blood levels met or exceeded a predicted target therapeutic range throughout the 24 hour dosing interval.

Inhibition of the target enzyme, plasma kallikrein, was measured in a sensitive and specific bioassay. Daily dosing with BCX7353 strongly inhibited plasma kallikrein at all four dose levels; the degree of inhibition was dose-related ($p < 0.0001$) and inhibition was sustained throughout the 24 hour dosing interval. This pharmacodynamic effect correlated strongly to achieved drug concentration ($r = 0.91$, $p < 0.0001$).

"We are very pleased that our first-in-human trial of BCX7353 met all of its objectives. The results show '7353 to be generally safe and well tolerated, and the observed drug exposure and kallikrein inhibition reaffirms our expectation that '7353 has the potential to be a once-daily treatment to wipe out HAE attacks," said Jon Stonehouse, CEO & President of BioCryst. "We are excited to now have the opportunity to test this promising drug in patients with HAE."

A Phase 2, four week dose ranging trial to evaluate the safety,tolerability,pharmacokinetics,pharmacodynamics, and efficacy of BCX7353 as a preventative treatment to reduce the frequency of attacks in HAE patients is expected to begin by late 2015 or early 2016.

Overall, 94 healthy volunteers were enrolled, and 92 completed the study. In the single dose part of the study, 34 subjects received a single dose of BCX7353 ranging from 30 mg up to 1000 mg, and 10 subjects received a single dose of placebo. In the daily dosing part of the study, 30 subjects received BCX7353 daily for seven days (10 each at 125 mg, 250 mg, and 500 mg per day), 10 subjects received 350 mg of BCX7353 daily for 14 days, and a total of 20 subjects received daily doses of placebo

(Source: BioCryst)

16
Oct, 2015

The United States Food and Drug Administration (FDA) has granted Fast Track designation for the investigation of Cinryze® (C1 esterase inhibitor [human]) for intravenous administration in subjects with Antibody Mediated Rejection (AMR) in renal transplant recipients. Cinryze is being studied as an adjunct treatment to Donor Specific Antibodies (DSA) reduction therapy in kidney transplant patients with acute AMR.

"There are currently no approved therapies for Antibody Mediated Rejection, a life-threatening and debilitating condition which can manifest in patients receiving kidney transplants," said Philip J. Vickers, Ph.D., Head of Research and Development at Shire. "The Fast Track designation represents an understanding of the significant unmet medical need for this condition. Shire looks forward to working closely with the FDA as we continue to study Cinryze as a potential treatment option for these patients."

Shire is planning a Phase 3 multi-center, multi-national, randomized, double-blind, placebo-controlled study (SHP616-302) to evaluate the efficacy of Cinryze (intravenous administration) as an adjunct to DSA reduction therapy (plasmapheresis, plasma exchange, and/or immune adsorption treatments and IVIG) for the treatment of acute AMR in kidney transplant recipients. The trial will be conducted in the United States, Europe and Canada and the study will open for enrollment by the end of October 2015.

The FDA's Fast Track program is designed to facilitate the development and expedite the review of drugs that address serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. Fast Track designation may provide increased opportunities to interact and meet with FDA, and potentially increases the likelihood of being eligible for priority review if relevant criteria are met.

Cinryze is currently only approved for, and should only be used to treat, routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE.

(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 worldwide

Currently you will find HAE member organizations in 49 countries:

North America (2): Canada, United States of America

Central America (3): Costa Rica, Mexico, Puerto Rico

South America (8): Argentina, Brazil, Chile, Colombia, Ecuador, Peru, Uruguay, Venezuela

Europe (25): Austria, Belarus, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Macedonia, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, The Netherlands, Ukraine, United Kingdom

Middle East (3): Israel, Turkey, United Arab Emirates

Africa (1): Kenya

Central Asia (1): Russia

South Asia (1): India

East & Southeast Asia (3): China, Japan, Malaysia

Australia/Oceania (2): Australia, New Zealand

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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