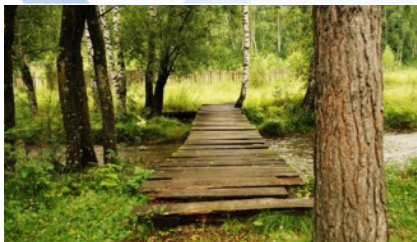




HAEi Newsletter



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A Message from the President

Dear HAEi Friends,

It is exciting that we are now celebrating our **hae day :-)** number four. Please visit the new **hae day :-)** website at www.haeday.org and help cover the world with smiles!

hae day :-) provides a perfect opportunity for HAEi to step back and assess the global picture when it comes to HAE awareness and access to treatment. The growth of HAEi and effective advocacy work being performed by member organizations is making an important difference in the lives of HAE patients.

Despite great progress, we must be mindful that the state of global HAE management remains less than satisfactory as evidenced by survey responses from member organization countries:

- 40 percent rate HAE as having severe negative impact on the lives of patients,
- 25 percent have no modern therapies registered nor reimbursed, and
- 80 percent noted that patients have limited or no influence on their choice of therapy.

HAEi is highly motivated to help member organizations as they work to improve patient quality of life. Because advocacy flourishes when people can freely interact and share ideas, going forward, our Facebook page will be the place where the HAEi family can meet and share information. In addition,

HAEi has a wide variety of initiatives planned for the second half of the year that will include (1) organizing patient workshops in regions where there are newer member organizations, and (2) broadening the technical assistance and tools member organizations can use to identify more patients and sharpen advocacy activities aimed at improving access to therapy.

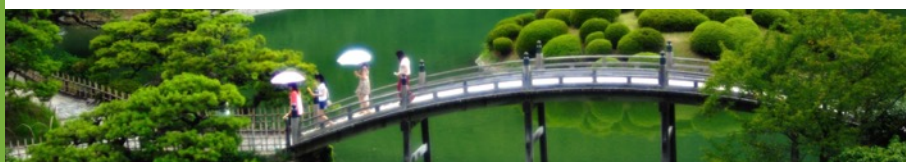


As a united HAEi family, we will find ways to achieve our dreams of a better life!

Happy **hae day :-)**

Warm regards,

Anthony J. Castaldo
President, HAEi



Plans for an exciting HAE Global Conference

Following the very successful HAE conferences in Copenhagen, Denmark in 2012 and Washington D.C., USA in 2014, HAEi is delighted to announce that the third HAE Global Conference will be held in Madrid, Spain in 2016.

After announcing the venue, HAEi Executive Director Henrik Balle Boysen offered the HAEi family highlights of what is being planned for the 2016 global conference:

“Attendees 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.”

HAEi expects the conference to be attended by approximately 550-600 delegates - including patients, care givers, physician/researchers, other healthcare professionals, and industry representatives - from all over the world.

All conference sessions and social events will take place at the conference venue, Hotel Auditorium Madrid. The hotel is conveniently located right next to Madrid-Barajas Airport.

Henrik Balle Boysen said, “Together with Camilla Müller from our conference partner, ConferenceCare, Executive Committee member Sarah Smith Foltz and I have inspected the facilities. It’s a remarkable venue that has the largest combined hotel and conference capacity in Europe. The hotel has recently entered an

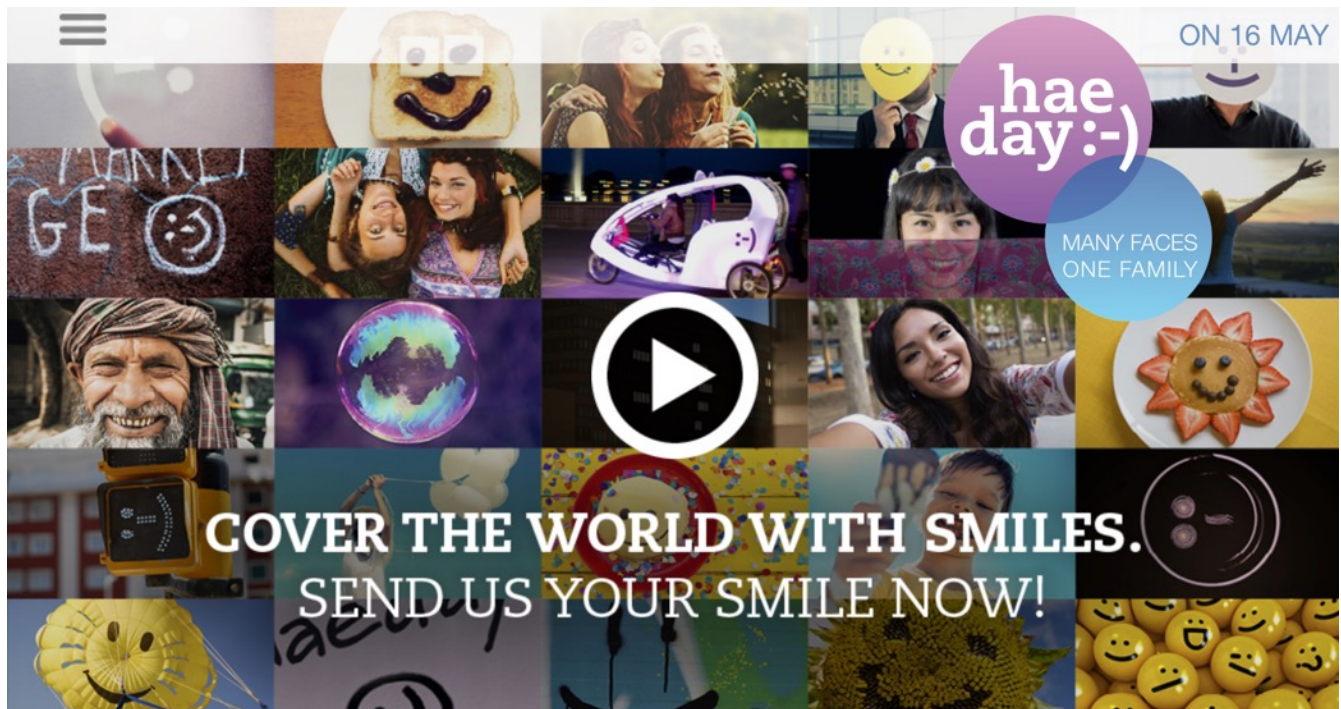


agreement to become a Marriott hotel, therefore a complete face-lift of the hotel is currently taking place.”

The dates for the HAE Global Conference in Madrid are 19-22 May 2016.

Henrik Balle Boysen also said, “As usual, the HAE Global Conference offers a blend of work and social/networking opportunities. The Scientific Program and a HAEi Executive Committee meeting will take place on Thursday afternoon 19 May 2016. 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 sight-seeing tour of Madrid.”





Introducing two new websites

In late March 2015 HAEi introduced a new version of the **hae day :-)** website www.haeday.org that supports the annual global awareness campaign. HAEi is proud to announce that the HAEi website www.haei.org is launched on **hae day :-)** 2015.

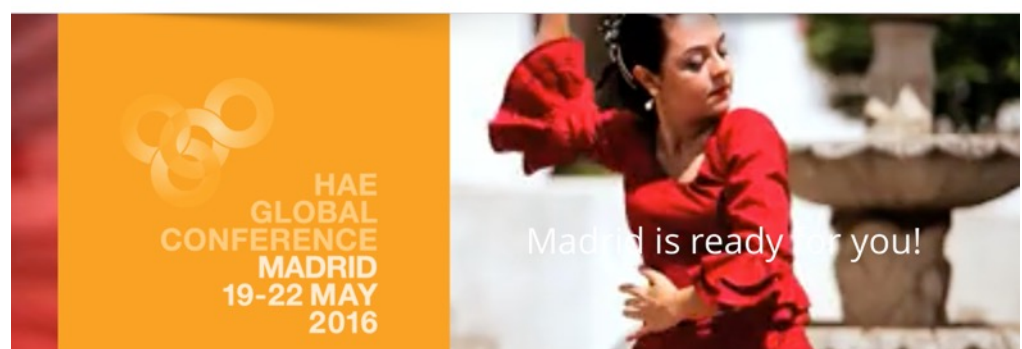
The **hae day :-)** website features an updated version of the annual 'Cover the World With Smiles' campaign, and offers a toolbox to assist member organizations in their effort to raise HAE awareness. In addition, the website includes patient stories, a short movie on the smiles campaign, and acknowledgment of the **hae day :-)** 2015 supporters: Shire, BioCryst Pharmaceuticals, Pharming Group, Dyax Corp. and CSL Behring.

HAEi Communications Manager Steen Bjerre said, "The new HAEi website is quite different from the previous one. It is far more visual and HAE information is presented in a more appealing manner. The new website offers a comprehensive overview of key HAE information including treatments, but is much easier to navigate and get to what you might be interested in seeing. Over the next several months we expect to roll out the HAEi website versions in French, German, Italian, Russian, and Spanish. We hope to add further languages later in 2015 and 2016."

The new HAEi website contains news and information about the global organization and the member organizations, a calendar that shows global HAE events, and an archive of past HAEi newsletters. It also includes a Resources Section with information on HAE treatments, patient stories, advocacy materials, recent medical journal publications, treatment recommendations/consensus documents, and HAE-related videos.

HAEi friends who travel will be happy to know that the new website contains a world map with information on each member country's care centers, hospitals, physicians, and available medication.

The new version of www.haei.org also provides the HAEi family with an elegant and user friendly environment for hosting their websites under the HAEi umbrella. HAEi is offering this service free of charge for the National Member Organizations and National Patient Groups.



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:



- **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>
- **Firazy® 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 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>

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>



HAE NEWS FROM AROUND THE GLOBE

From our National Member Organizations



Australia and New Zealand (www.haeaustralasia.org.au)

From Fiona Wardman, President of HAE Australasia:

Lobbying: HAE Australasia have been lobbying our local Members of Parliament to create awareness of HAE Australasia, HAE and our pre budget submission to the Government for funding. The funding will go towards a patient registry, annual patient meetings and website hosting costs. We hope to be successful with the entire amount we are asking for, but will have to wait and see. By reaching out to our local Members of Parliament we have made some great contacts, and hope they will continue to be champions for our cause in the future.

Media campaign: We hope to launch a media campaign - dependent on funding - for **hae day** :- leading up to our patient meeting, that takes place 16 May 2015 at Novotel Sydney Olympic Park, Olympic Boulevard, Sydney.

New resources: HAE Australasia have created some new resources for our patients. We have a new brochure explaining what HAE Australasia is about, and the brochure 'Someone in my family has been diagnosed with HAE', which offers information on what HAE is, what causes HAE, triggers, warning signs and symptoms.

Education session: One of our families attended an education session organized by the head of the Emergency Department at one of the major hospitals in Brisbane where they were able to tell their story to medical students and registrars etc. The education session was accessed by several campus' and locations.

Rare Disease Summit: I recently attended a Rare Disease Summit in Melbourne - a fantastic event bringing together patients, patient organizations, clinicians, government health departments and others with an interest in the care of patients with rare diseases to create a National Plan for Rare

Diseases. The summit was organized by Rare Voices Australia and they are calling for the Federal Government to adopt a national approach to rare diseases.



Belgium (www.hacbelgium.be)

8 May 2015 the Belgian HAE organization held a congress with Prof Hermans and Doctor Lambert in Brussels. More than 35 patients and family members took part.



Canada (www.haecanada.org)

From Timothy Howe, Executive Director of HAE Canada:

Upcoming Patient Events: We will be holding patient events in Toronto (23 May), Edmonton (13 June), and Calgary (17 October). The guest speaker are Dr. Stephen Betschel MD, FRCPC (Toronto), Dr. Bruce Richie MD, FRCPC (Edmonton), and Dr. Tom Bowen MD, FRCPC (Calgary). For more information or to RSVP, please contact John Sloat at jsloat@haecanada.org.

Membership Kits: We are pleased to announce that we have finalized the content for our membership kits. Kits will be sent to all current members and to new members upon joining HAE Canada. The kit contains valuable information and resources that we feel help to increase the value proposition for our membership. Membership in HAE Canada is free and is open to HAE patients, their families, friends and caregivers who reside in Canada. To become a member please visit our website at www.haecanada.org.

HAE Canada Website Upgrade: Work is well underway on upgrading our website to improve functionality and to make it more appealing on mobile devices. Included in this upgrade is the creation of a members only section and secure members forum. More details about this initiative to come.

Awareness day: We have some tricks up our sleeves for **hae day** :- 2015, so please watch www.haecanada.org and our Facebook page [www.Facebook.com/HAECanada](https://www.facebook.com/HAECanada).


Czech Republic (www.hae-imuno.cz)

On 23 April 2015 the NGO Forum 2000 took place in Prague. The HAE organization in Czech Republic participated in order to raise awareness about the organization and HAE.


Denmark, Norway and Sweden (www.haescan.org)

HAE Scandinavia will be holding the first Scandinavian conference on 6-8 November 2015. The venue will be in Denmark.


Germany (www.angioedem.de)

Patient day: 24 April 2015 the German HAE organization held a patient day at Universitätsklinikum Frankfurt. On the agenda were items such as activities for youngsters organized by the German HAE

organization, new development within HAE research and the future of HAE therapy.

Awareness day activities: On **hae day** :- 2015 the German HAE organization will launch an event at Cologne central station. Supported by Shire GmbH the German organization will draw attention to HAE but also auction a number of large 3D images by the artist Ella Mundt from Bad Ems. The activities began already on 15 May with a press conference, also at the central station in Cologne. One more awareness project in Germany is 'HAErkules - Kids and Teens Strong Together', supported by CSL Behring.


Hungary (www.haenet.hu)

The 9th C1-Inhibitor Deficiency Workshop in Budapest is scheduled for 28-31 May 2015. The conference focuses on bradykinin-mediated angioedemas, and particularly on the types resulting from

C1-inhibitor deficiency. The topics covered by the four-day long event are, among others, the latest achievements in the diagnostics of the disease, exploration of its hereditary, pathogenetic, and clinical background as well as the management and follow up of the patients. See more on the conference at www.haenet2015.hu.


Japan (www.haej.org)

HAE Japan is holding a meeting in Tokyo on **hae day** :- 2015 to exchange information and to talk about what has been achieved over the past year since becoming a national member

organization. HAE Japan will also be holding its first General Meeting for members.

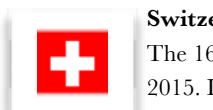

Macedonia (www.haemacedonia.mk)

The SEE HAE Workshop was held on 3 April 2015 in Skopje in organization of Prof. Vesna Grivcheva-Panovska. The most prominent European experts in the field of HAE - among them Prof. Cicardi,

Prof. Farkas, and Dr. Varga - as well as regional HAE experts presented up to date methods of diagnostics, treatment and prevention of HAE. For the first time, experts from Slovenia, Croatia, Montenegro, Serbia, Albania, Kosovo, and Macedonia united in order to establish the SEE HAE Committee, to establish mutual cooperation and to unify sustainable diagnostics and treatment procedures in a form of SEE HAE Consensus for all countries of the region. The book of abstracts from the workshop can be downloaded from <http://mediskop.org.mk/book-of-abstracts>


Spain (www.angioedema-aedaf.org)

AEDAF held its 17th annual meeting and general assembly on 18 April 2015 at Hospital Universitario La Paz in Madrid.


Switzerland (www.hae-vereinigung.ch)

The 16th HAE Patient Meeting took place 25 April 2015. In connection with the meeting the participants had the opportunity to visit the Paraplegiker-Zentrum in Nottwil.


United Kingdom (www.haeuk.org)

Information booklet: HAE UK has sent out copies of the new HAE Patient Information Booklet to all members and all HAE consultants and specialist nurses in the UK.

The organization encourages all patients in the UK to register with HAE UK so they can get copies of the booklet, which will help when explaining to employers, schools and friends.

Emergency card: HAE UK is working on an accident & emergency card, which will be a personal identification card and can be carried in the patient's purse to be used in an emergency. Hopefully HAE UK will be able to launch the card in the coming months.

Addenbrooks meeting: The Care Quality Commission held a public meeting in Cambridge 21 April 2015 for all Addenbrookes Hospital's Allergy Department Patients to share their experiences of services provided by the hospital. Ann and John Price attended the meeting to try to get home therapy services for HAE patients under the care of the Allergy consultants.

Patient Day: This year's HAE UK patient day will be held in Birmingham on 7 November 2015.



USA (www.haea.org)

HAE app: The US HAEA is excited to announce that the myACT app (Access to Continued Therapy) is now available to help patients easily store information needed to successfully manage their HAE. The myACT app is ready now for the android base operating system. An iOS version of the app is currently in development - please see the US HAEA website for information regarding release date.

Opportunities to connect: The US HAEA is very visible on the social media - be sure to check out all of the resources available to connect:

- **Facebook:** <https://www.facebook.com/hereditaryangioedema>
- **US HAEA's Twitter:** https://twitter.com/US_HAEA
- **Tony Castaldo's Twitter:** <https://twitter.com/TonyJCastaldo>
- **Instagram:** https://instagram.com/us_haea



US HAEA Scientific Registry: The US HAEA Scientific Registry is celebrating its 5th year anniversary - actually it started in January and it will continue throughout the year. Scientific Registry members were treated to five year anniversary celebration

items including glass paperweight prizes for excellence in reporting, award mugs for five year members, and Anniversary cards for all Registry members.

The invitation has gone out again via US HAEA social media channels to join the scientific registry. It is easy, it is free - and it is done at <http://www.haea.org/get-involved/us-haea-scientific-registry>.



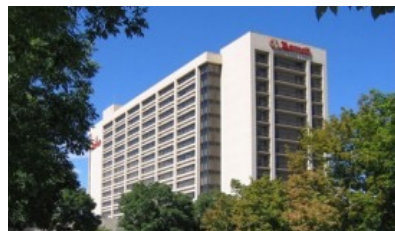
HAE on the Hill: 22 April 2015 the US HAEA President, Anthony J. Castaldo, joined Dana Kuhn, President of PSI (the organization that helps pay for HAE medications) on Capitol Hill in Washington D.C.

where they met with members of the US Congress to explain how this vitally important program benefits patients with HAE and other rare diseases. Among others Dana Kuhn and Anthony J. Castaldo spoke with Congressman Dave Brat (centre) from Virginia.

Now on Facebook: As part of the ongoing commitment to empowering patients by providing real-time information and updates related to HAE, the US HAEA has launched an official Facebook page. The page is for the US HAEA community to enjoy and make use of as a resource for on-going communication and outreach. It will contain posts of all of the HAEA's advocacy efforts, including **hae day** :-)) news and events, public policy

initiatives, industry news, research updates, etc. Take a moment to "Like" the page so that you can stay informed and feel free to share - see www.facebook.com/hereditaryangioedema.

Large scale study: The US HAEA Angioedema Center is initiating a large-scale project to study HAE with normal C1 inhibitor. Further details about the project and how to participate will be forthcoming over the next several months.



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.

Scholarship Program: The Fall 2015 US HAEA Scholarship Program recipients have been selected and notified.

The US HAEA has declared 2015 the Year of the HAEA Youth and in support of the HAEA younger generations the organization has announced the HAEA Scholarship Fund. The program will provide financial support for young HAE patients seeking to improve their lives through academic achievement. It is available to US citizens with a confirmed HAE diagnosis (letter from a licensed physician) who will be enrolled in an undergraduate educational institution in the fall of 2015.

Scholarships has been awarded based on a combination of financial need, academic effort, and individual educational goals. A big congratulations to all recipients :-)



From our National Patient Groups



Belarus (www.hereditary-angioedema.org)

The first ever workshop aimed at patients/physicians in Belarus and CIS - the organisation of former Soviet Republics - took place in Minsk 24-26 April 2015.



HAEi participated in and presented at the workshop and had the opportunity to cooperate with patients and doctors taking steps to form an advocacy organization. The Belarus HAE group aims to raise awareness, increase diagnosis, and gain access to modern HAE medicines.



United Arab Emirates

([www.facebook.com/groups/-111656808988882/?fref=ts](https://www.facebook.com/groups/111656808988882/?fref=ts))

The HAEi representative in the Middle East, Mr. Rashad Matraji, writes that still more patients are being identified and diagnosed in the United Arab Emirates. Also, there are now two medications available in pharmacies, Berinert and Kalbitor, but they are not registered yet.



Peru (www.facebook.com/Angioedema-HereditarioPeru)

In Peru Mrs. Suzet Lam Torres is presently working on the formal approval of the Peruvian HAE organization, Asociación Peruana de Angioedema Hereditario. The organization already has three honorary members:

- Dr. Alfredo Berrocal Kasay, Rheumatologist and immunologist at Hospital Nacional Cayetano Heredia and Director of Departamento de Investigación en Medicina at Universidad Cayetano Heredia,
- Dr. Alfredo Guerrero Benavides, Neurologist and Medical Director of Clínica Internacional,
- Dr. Oscar Calderon, Allergist at Clínica Limatambo.

HAE is on the Peruvian Ministry of Health's list of patients with rare diseases.

Ask the doctors

The US HAE Association recently implemented a new process for answering patient's 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 questions - and the answer from the expert physician, Dr. Bruce Zuraw.

Question:

Why does the effectiveness of certain treatments vary among patients with HAE? Why do some treatments work well for prophylactic use and others for acute attacks?

Answer:

This is really two separate questions. Starting from the last, you ask why some treatments work to prevent attacks (prophylactic) and others to treat acute attacks (on-demand). This is really a matter of timing. If you could absolutely predict when an attack would occur, than all of the new HAE medicines would work as prophylactic treatment. However, since we cannot predict exactly

when attacks will occur, the prophylactic medicines (such as C1 inhibitor) must be able to stay in the body long enough to provide continuous or near-continuous prevention. The medicines that are not used for prophylaxis (icatibant and ecallantide) do not stay in the body long enough to work in this way.

Now the first question is more difficult to answer and needs to be addressed on two levels. The first or highest level answer is that icatibant only works to prevent bradykinin from binding to its receptor. Therefore, the angioedema must be caused by bradykinin. While we know that HAE due to C1 inhibitor deficiency causes angioedema due to bradykinin, the cause of HAE with normal C1 inhibitor is not yet known. In fact, what we call HAE with normal C1 inhibitor may be a collection of different diseases some of which may be due to bradykinin but others not due to bradykinin. On the second level, there can be many reasons why icatibant does not work for all bradykinin mediated attacks of angioedema. For instance, it can be given too late in the attack. In addition, we suspect that there are genetic differences between people that determine how well a specific drug may work in them. This is an area that requires further research.

Global Advocacy Work



Recent activities

This is a brief overview of some of HAEi's activities in the recent months:

In March 2015 HAEi participated in the annual conference 'International Plasma Protein Conference – IPPC 2015', organized by Plasma Protein Therapeutic Association (PPTA). This time the conference was held in **Rome, Italy**. During the conference, HAEi attended patient advocacy meetings sponsored by PLUS (Plasma Users). Henrik Balle Boysen was elected to be part of the steering committee for PLUS for future activities.

The last few days of March HAEi was in **Manila, the Philippines** for a meeting with the President of the Philippine Orphan Drug Society, the President of the Philippine Society of Allergy and Immunology Specialists, and the Director of the Philippine National Institutes of Health. These officials had expressed a keen interest in helping HAEi establishing a NPG in the Philippines as well as in other countries in the region.

Early April HAEi participated in the first regional workshop for the Balkan's taking place in **Skopje, Macedonia**. Dr. Grivcheva-Panovska from Macedonia coordinated this physician-focused workshop. Although it was a good opportunity to meet physicians

from the Balkan area there was unfortunately allocated way too little time for this conference. HAE Macedonia is keen on arranging a more patient focused workshop later this year and HAEi has already dedicated resources for that purpose.

Later on in April HAEi participated in and presented at the first Belarusian and CIS HAE Workshop in **Minsk, Belarus**.

Future activities

15-17 May HAEi will take part in the national HAE Australasia meeting to be held in **Sydney, Australia**.

At the end of May HAEi will be represented at the 9th C1-inhibitor workshop in **Budapest, Hungary**. This is the longest running (the inaugural meeting took place in 1999) and most important scientific meeting solely dedicated to HAE.

7-10 June HAEi will be in **Barcelona, Spain** participating in this years EAACI conference. The event is expected to be a great opportunity to catch up both with healthcare professionals and industry.





NEW PAPERS ON HAE

Here are summaries of some of the HAE related scientific papers published since our last newsletter:

Clinical manifestations, diagnosis, and treatment of HAE: survey data from 94 physicians in Japan - by I. Ohsawa et al., Juntendo University Faculty of Medicine, Tokyo, Japan:

Data on 171 HAE patients were collected from 94 physicians (24.3% response rate). Of the patients, 76.6% had a family history of angioedema, and 11.7% had experienced a death in the family due to an angioedema attack. HAE is a severe condition characterized by recurrent angioedema attacks. In Japan, delayed patient diagnosis and limited use of HAE-specific therapies exacerbate the burden on HAE patients. (*Ann Allergy Asthma Immunol.*, April 2015)

Perioperative management for patients with HAE - by A.H. Williams and T.J. Craig, Midwestern University, Downers Grove, Illinois, USA:

Preventing attacks particularly for patients undergoing procedures is critical. HAE-patients may now treat acute attacks or prevent attacks with medications that have recently become available in USA; however, these same medications can be used for perioperative management for patients undergoing medical, surgical, and dental procedures. Periprocedural planning is important for patients to reduce the incidence of acute attacks. Education is critical and increasing awareness of short-term prophylaxis options will allow providers to develop an appropriate action plan for their patients. The availability of treatment options has increased over the past few years, expanding options for physicians and HAE-patients and improving safety during the perioperative period and at the time of other procedures. (*Allergy Rhinol (Providence)*, January 2015)

The autoimmune side of hereditary angioedema: insights on the pathogenesis - by P. Triggianese, University of Rome, Italy, et al.:

Occasional reports link HAE with autoimmune conditions and only few studies have been conducted on large patient populations with controversial results. Although several immunoregulatory disorders have been documented, the prevalence of defined autoimmune diseases in HAE-patients remains debated. The occurrence of autoimmune conditions in HAE patients may worsen the disease severity enhancing the complexity of the comprehensive care. (*Autoimmun Rev.*, March 2015)

Efficacy of C1 esterase inhibitor concentrate in treatment of cutaneous attacks of HAE - by K. Bork et al.:

The average attack duration per patient of all cutaneous attacks or facial and peripheral cutaneous attack subsets was significantly faster with C1-INH treatment than without treatment. Mean average attack durations per patient for all, facial, and peripheral attacks were 2.04, 1.45, and 2.16 days, respectively, in the C1-INH-treated group, and were 3.74, 4.45, and 2.98 days, respectively, in the untreated group. Treatment of cutaneous HAE attacks (all attacks or facial and peripheral attack subsets) with 20 IU/kg C1-INH concentrate provided faster attack resolution compared with no treatment. (*Allergy Asthma Proc.*, March 2015)

Prevalence of HAE in untested first-degree blood relatives of known subjects with HAE - by M.A. Riedl et al.:

Patients with a confirmed diagnosis of HAE recruited first-degree relatives who had not been evaluated for HAE. Enrolled subjects underwent complement testing. If the lab tests were abnormal, the enrolled subjects returned to the site for a follow-up visit and questionnaire. Overall, 31 patients with HAE and 46 first-degree relatives enrolled in the study. Of 46 enrolled relatives, 65% had lab test results that ruled out a diagnosis of HAE, 4% were categorized as 'HAE not ruled out', and 30% were newly diagnosed with HAE. Of 14 newly diagnosed subjects, nine reported having experienced symptoms that may have been related to HAE, such as swelling in the throat, face, or extremities or abdominal pain. When reported, median age of symptom onset in these 14 subjects was nine years whereas newly diagnosed asymptomatic subjects had a median chronological age of six years. These 14 subjects reported a historic mean standard deviation rate of 2.51 (5.59) swelling episodes per month with a mean standard deviation duration of 1.6 (0.74) days. This study reinforces the importance of testing family members of patients with HAE to detect this hereditary condition. (*Allergy Asthma Proc.*, March 2015)

A randomized trial of icatibant in ACE-inhibitor-induced angioedema - by M. Bas, Technische Universität München, Germany, et al.:

Among patients with ACE-inhibitor-induced angioedema, the time to complete resolution of edema was significantly shorter with icatibant than with combination therapy with a glucocorticoid and an antihistamine. (*N Engl J Med.*, January 2015)



NEW PAPERS ON HAE

A nationwide survey of HAE due to C1 inhibitor deficiency in Italy - by A. Zanichelli, Università degli Studi di Milano, Ospedale Luigi Sacco, Milano, Italy, et al.:

This nationwide survey of C1-INH-HAE provides for Italy a prevalence of 1:64,935. C1-INH-HAE patients listed in the database have a shorter life expectancy than the general population. An increased awareness of the disease is needed to reduce this discrepancy. Measurement of C4 antigen can exclude diagnosis of C1-INH-HAE with an accuracy > 95%. This parameter should therefore be considered for initial screening in differential diagnosis of angioedema. (*Orphanet J Rare Dis.*, February 2015)

Safety of C1-esterase inhibitor in acute and prophylactic therapy of HAE: findings from the ongoing international Berinert patient registry - by P. Busse, Mount Sinai Hospital, New York, USA, et al.:

The plasma-derived, pasteurized C1-inhibitor (C1-INH) concentrate, Berinert has a 4-decade history of use in HAE, with a substantial literature base that demonstrates safety and efficacy. Thromboembolic events have rarely been reported with C1-INH products, typically with off-label use or at supratherapeutic doses.

A registry was initiated in April 2010 at 27 US and 4 EU sites to obtain both prospective and retrospective safety and usage data on subjects who were administered C1-INH (Berinert). This large pool of real-world clinical usage data in HAE further supports the extensive safety profile of two Berinert formulations when used on demand and/or for prophylaxis in both home and health care settings. No evidence was found to suggest that Berinert is an independent, causative risk factor for thromboembolic events. (*J Allergy Clin Immunol Pract.* March-April 2015)

Current medical management of HAE: follow-up survey of US physicians - by M.A. Riedl, Li, University of California, San Diego, California, USA, et al.:

A physician survey conducted in USA between October 2009 and February 2010 revealed wide variability in HAE management. A follow-up survey was conducted to assess the impact of newly available treatment options and investigate changes in HAE care patterns. Analysis of these findings suggests that the change in HAE treatment has increased self-treatment at home, decreased emergency department visits and/or hospitalizations, and

provided greater patient satisfaction. (*J Allergy Clin Immunol Pract.* March-April 2015)

HAE with a focus on the child - by G. Bennett and T. Craig, Penn State University, Hershey, Pennsylvania, USA:

HAE symptoms often appear early in life and accelerate around puberty. Despite this, there is a paucity of both data and treatment options for HAE in children in USA. A search of electronic medical records from 2001 to 2011 was performed for children aged 1 to 18 years with a confirmed diagnosis of HAE. 25 pediatric HAE-patients were identified: 13 female and 12 male. The median age at diagnosis was seven years. The most common initial presenting symptom was swelling of the upper extremity, followed by abdominal pain, swelling of the face and/or lower extremity, and scrotal swelling. Three patients reported no previous symptoms and were diagnosed due to family history of HAE and positive laboratory testing. 84% of patients reported a family history of HAE. Accurate and timely diagnosis of HAE is imperative for children to prevent further morbidity and mortality associated with the disease. (*Allergy Asthma Proc.*, January-February 2015)

Presence of C1-inhibitor polymers in a subset of patients suffering from HAE - by D.E. Madsen, University of Southern Denmark, Esbjerg, Denmark, et al.:

To investigate the presence of C1-inh polymers in patient plasma samples, an immunological method was developed, where monoclonal antibodies produced against polymerized C1-inh were applied in native PAGE western blotting. Genuine plasma samples from 31 Danish HAE families were analyzed, and it was found that plasma samples from three genotypically distinct HAE type I families contained C1-inh polymers. Identical C1-inh polymerization phenotypes were observed in four affected family members from one of these families. Genotyping of the families revealed that the polymerogenic mutations of two families were located in proximity to the reactive center loop insertion site in C1-inh, and one mutation affected helix C. It was demonstrated that C1-inh polymers are present in the plasma of a subgroup of HAE type I patients. (*PLoS One.* November 2014)

News from the Industry



PHARMING

19 March 2015

Pharming Group N.V. has nominated Paul Jai Sekhri and Jan Hendrik Egberts as members of the Board of Supervisory Directors.

The nominations will be subject to shareholders' approval at the Annual General Meeting of Shareholders.

Mr. Sekhri (1958) has over 28 years of operational experience in life sciences with in-depth knowledge of multinational pharmaceutical and biotechnology markets and products. Mr. Sekhri is currently Chief Executive Officer of Lycera Corp., a biopharmaceutical company developing breakthrough medicines to treat cancer and autoimmune disease. Prior to joining Lycera, Mr. Sekhri was Senior Vice President, Integrated Care at Sanofi, where he led the creation of innovative solutions and business models to meet patient needs. Previously, he served as Group Executive Vice President, Global Business Development and Chief Strategy Officer at Teva Pharmaceutical Industries Ltd. Mr. Sekhri has held positions in small biopharmaceutical companies, large and small pharmaceutical companies, and venture capital/private equity firms, including TPG, Cerimon Pharmaceuticals, Ariad Pharmaceuticals and Novartis AG. Mr. Sekhri completed postgraduate studies in clinical anatomy and neuroscience at the University of Maryland, School of Medicine and received his BSc degree from the University of Maryland.

Mr. Egberts (1958) has over 25 years of executive experience in the pharmaceutical and medical device sectors, most recently as Chief Executive Officer at Agendia Inc., a molecular diagnostics company. Prior to this, Mr. Egberts was Chief Executive Officer of OctoPlus N.V., a specialty pharmaceutical company, which was acquired by Dr. Reddy's Laboratories Ltd. in 2013. Mr. Egberts also served as a senior healthcare advisor for 3i Group plc, a private equity firm and as President, Chairman and Chief Executive Officer of NovaDel Pharmaceuticals Inc., where he developed a portfolio of pre-clinical and clinical compounds, gaining FDA approval for two compounds. In addition, Mr. Egberts has held multiple business development and general management positions at Johnson & Johnson, Merck & Co. and Mölnlycke Health Care. Mr. Egberts graduated from Erasmus University Medical School in the Netherlands and he obtained his MBA from Stanford after which he worked as a management consultant for McKinsey & Co. Mr. Egberts continues to serve on the supervisory board of CHDR (Center for Human Drug Research) and Implanet SA.

The Chairman of Pharming's Board of Supervisory Directors, Jaap Blaak, said: "We are delighted that our Board may be strengthened with two highly qualified professionals, who have vast experience and networks in the Pharma and Biotech business, both in Europe and the US. We believe both Paul and Jan will be valuable assets for Pharming. In particular, their expertise in developing and commercialising products and business development will help us build a financially sustainable enterprise with a pipeline beyond the Ruconest franchise and I look forward to working with them to achieve this."



31 March 2015

Dyax Corp. has announced positive safety, pharmacokinetic, biomarker, and efficacy results from the Phase 1b clinical study of their investigational product, DX-2930. Discovered by

Dyax, DX-2930 is a fully human monoclonal antibody inhibitor of plasma kallikrein being developed for the prevention of HAE attacks.

The ongoing Phase 1b study is a multi-center, randomized, double-blind, placebo-controlled, multiple-ascending dose study designed to assess the safety, tolerability and pharmacokinetics of DX-2930 in HAE patients. An analysis of HAE attack rate was also conducted following a pre-specified statistical analysis plan. A total of 37 subjects were randomized to active drug or placebo in a 2:1 ratio across 4 dosing groups of 30, 100, 300, or 400 mg. Each subject received two doses of DX-2930 or placebo, separated by 14 days, and was followed for 15 weeks after the second dose. DX-2930 was well tolerated at all dose levels. There were no deaths or subject discontinuations due to an adverse event. There were no serious adverse events in subjects treated with DX-2930 and no evidence of dose-limiting toxicity. There was no safety signal in treatment-emergent adverse events, clinical laboratory results, vital signs, or electrocardiograms. Subcutaneous injection was well tolerated. Pharmacokinetic results demonstrated that DX-2930 has linear, dose-dependent exposure and a mean elimination half-life of approximately 14 days across all dose groups studied. Pharmacodynamic results from two different exploratory biomarker assays confirmed ex vivo plasma kallikrein inhibition in a dose- and time-dependent manner. Primary proof-of-concept efficacy analyses were based on subjects in the 300 mg, 400 mg, and placebo dose groups who reported having at least 2 attacks in the 3 months prior to study entry. During the pre-specified, primary efficacy interval of 6

News from the Industry



weeks (from days 8 to 50; corresponding to peak drug level), the HAE attack rate (adjusted for baseline attacks) was 0 in the 300 mg group and 0.045 attacks per week in the 400 mg group, compared to 0.37 attacks per week in the placebo group. This resulted in a 100% reduction for the 300 mg dose group as compared to placebo ($P < 0.0001$), and an 88% reduction for the 400 mg dose group as compared to placebo ($P=0.005$). During this primary efficacy interval, 100% of subjects in the 300 mg group ($P=0.026$) and 82% of subjects in the 400 mg group ($P=0.030$) were attack-free compared with 27% of subjects in the placebo group. The study will be complete when all subjects in the 400 mg dose group finish the final safety assessments on study day 120.

Dyax also announced receipt of Fast Track designation from the U.S. Food and Drug Administration (FDA) for the investigation of DX-2930 for HAE.

“These data provide important clinical proof-of-concept, dose response and safety information in the target patient population,” said Burt Adelman, M.D., Executive Vice President of Research and Development and Chief Medical Officer at Dyax. “The study met all of its primary objectives, and notably, DX-2930 also demonstrated statistically significant reductions in attack rate compared to placebo, an important characteristic for a prophylactic treatment. We look forward to communicating these results to the FDA to ensure that our product development plan is supportive of drug approval. We plan to take full advantage of the opportunities that Fast Track designation allows in order to maximize the possibility of a more rapid path to approval.”

“The positive results from this trial are a significant milestone for Dyax and will be integral in guiding the future clinical development of DX-2930,” said Gustav Christensen, President and CEO of Dyax. “If approved, we believe that DX-2930, with its unique profile, is well positioned as a potential preventive treatment option for patients suffering from HAE.”

CSL Behring
Biotherapies for Life™

27 April 2015

Several European health authorities have completed the assessment of a new, low-volume presentation size for the existing indications of Berinert, a human plasma-derived, pasteurized,

and nanofiltered C1-esterase inhibitor (C1-INH) concentrate from **CSL Behring**. It is indicated for the treatment and pre-procedure prevention of acute episodes of HAE type I and II.

“This new vial size containing 1500 International Units of C1-esterase inhibitor is reconstituted with only 3mL of solvent and thus provides a new and convenient choice for patients of the appropriate body-weight”, said Prof. Markus Magerl M.D., Department of Dermatology and Allergy, Charité–Universitätsmedizin, Berlin, Germany. “As it can be prepared and administered faster than the same dose using the existing vial size of 500IU, we think it will be appreciated by many patients.”

The new Berinert 1500IU vial size will be available in several European countries following the respective national implementation phase. The existing vials size and formulation (Berinert 500IU) will also remain available.

“We believe that this new presentation of Berinert provides patients an additional choice that features all the known advantages of the existing product with additional practical and convenience attributes”, commented Debbie Drane, Vice President Global Commercial Development, CSL Behring. “Many patients will need fewer vials for the same dose, which not only saves time to treatment but also means less storage room, less ancillaries needed and less waste.”



29 April 2015

Dyax Corp. has announced financial results for the first quarter ended March 31, 2015. Recent highlights include:

- Reported positive safety, pharmacokinetic, biomarker and proof-of-concept efficacy results from the Phase 1b study of DX-2930 in HAE patients;
- Receipt of Fast Track designation from the U.S. Food and Drug Administration (FDA) for the investigation of DX-2930 for HAE;
- Kalbitor net sales were \$16.0 million for the first quarter of 2015.

“Dyax achieved several milestones in the early months of 2015”, said Gustav Christensen, President and CEO of Dyax.

“DX-2930, our lead development candidate being investigated for the prevention of HAE attacks, demonstrated impressive Phase 1b results. This study provided important clinical proof-of-concept, dose response and safety information in HAE patients. The Kalbitor business continue to generate cash flow which supports our development programs. We have made tremendous progress at Dyax and are well positioned for long-term growth.”

News from the Industry



PHARMING

30 April 2015

Pharming Group N.V. has published its (unaudited) financial report for Q1 2015 ended 31 March 2015.

From the financial highlights:

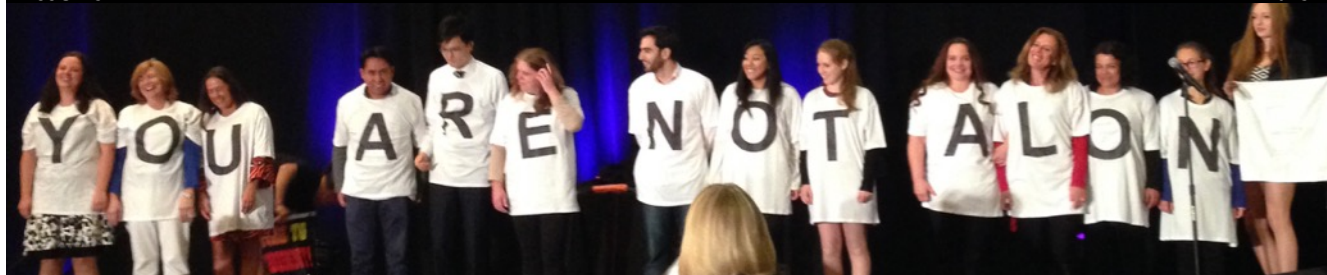
Ruconest sales in the US amounted to 0.6 million EUR and sales by Sobi in the EU amounted to 0.4 million EUR. Alongside Pharming realised initial direct sales in Austria, Germany and the Netherlands. Product sales in the first quarter of 2014 were a result of Sobi sales for the EU only.

From the operational highlights:

- Following the completed acquisition of Pharming's US partner, Salix, by Valeant Pharmaceuticals, the Ruconest US commercial infrastructure remains intact and commercialisation efforts remain 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 the quarter, creating the basis for continued revenue growth from sales in the US.
- Patient enrollment for the randomised double blind placebo controlled Phase II clinical trial to investigate Ruconest for the prophylaxis of HAE was initiated in January and continued during the quarter.
- In February, Dr. Perry Calias was appointed as Chief Scientific Officer. Calias will have 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.

Sijmen de Vries, Pharming's CEO, commented: "Pharming's performance during the first quarter of 2015 has started to reflect some of the transformational changes made in 2014. In particular, we have seen the beginning of increasing and profitable Ruconest sales in the US following the product launch in November. Also as result of these US sales and the first sales from the direct commercialisation of Ruconest in the EU, no additional impairments of inventories were incurred this quarter. We therefore expect revenues and gross profits to improve due to markedly improved sales during the remainder of the year."





HAEi around the globe

HAEi is a global network organization dedicated to raising awareness of C1 inhibitor deficiencies around the world.

Our **National Member Organizations (NMO)** are independent associations working for the benefit of patients in the specific country. Currently we have NMO's in 27 countries:

- **Asia:** Japan
- **Australia:** Australia, New Zealand
- **Europe:** Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Macedonia, Norway, Poland, Portugal, Spain, Sweden, Switzerland, The Netherlands, United Kingdom
- **North America:** Canada, Mexico, USA
- **South America:** Argentina, Brazil

Our **National Patient Groups (NPG)** are HAE patient representatives in countries where no formal association has yet been founded or where the process of

founding an association is starting up. Presently we have NPG's in 19 countries:

- **Africa:** Kenya
- **Asia:** China, India, Malaysia, Russia, United Arab Emirates
- **Europe:** Belarus, Bulgaria, Croatia, Ireland, Romania, Slovenia, Ukraine
- **South America:** Chile, Costa Rica, Equador, Peru, Uruguay, Venezuela

You will find much more information on the HAEi representations around the globe at www.haei.org. For instance, under each of the countries there is contact data for the national organization/group, information on care centers, hospitals, physicians, trial centers, and pharmaceutical companies as well as a list of available medication in the specific country.

The information on www.haei.org is being updated as soon as we receive fresh data from the NMO's or NPG's.

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](mailto:h.ballsen@haei.org) or Communications Manager [Steen Bjerre](mailto:s.bjerre@haei.org). 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.

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

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ONE FAMILY

