Issue 4 · September 2016

# HAEi Newsletter

## HAEi Youngsters

HAEi has a growing group of very engaged youngsters. They have a great network, they have fun together (like here at the HAE Global Conference 2016 in Madrid) - and they are searching for even better ways to control HAE in the future.

## 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 4 · August 2016**
Cover photo: From session in the Youngsters' track during the HAE Global Conference in Madrid 19-22 May 2016.
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# A Message from the President

**Dear HAEi Friends,**

Welcome to our September HAEi newsletter, which begins with excellent reports from our Regional Patient Advocates who are the dedicated and highly skilled individuals driving the effort to extend HAEi's global reach. The reports highlight the challenges and opportunities that confront HAEi friends in various countries throughout the world. In just about every situation, it appears that an organized, educated, and motivated patient advocacy group will be the lightning rod for achieving the goals shared by us all – broadening access to HAE medicines. We look forward to future reports of success as our Regional Patient Advocates provide assistance and support that enables patient groups to accelerate progress towards fulfilling their local objectives.

Its not too early to start thinking about **haeday :-)** 2017! As I am sure many of you will recall, HAEi and AEDAF (our Spanish member organization) organized a walk on the legendary Camino de Santiago as an **haeday :-)** event that led up to the 2016 HAE Global Conference in Madrid. The feedback from HAEi friends who took part in the walk was overwhelming with many describing the event as a phenomenal life experience. Based on the positive feedback, we are now in the process of organizing a Camino Walk as a global event for **haeday :-)** 2017. See page 16 for details.

As discussed in prior newsletters, the future for HAE patients looks positive because there are numerous clinical trials underway for new and/or improved HAE therapies. In addition, a variety of new companies are in early stage development of novel treatments. This level of interest in a micro orphan rare disease is extraordinary and is due, in large measure, to the fact that the global HAE community is organized, active, and shares an over arching goal of improving patient quality of life.

Needless to say, regulatory approval of a medicine doesn't mean anything until the therapy is available and reimbursed. My dear friends, time and time again, we see that no matter the odds being faced – creative, aggressive, and consistent advocacy creates the most effective path towards gaining access to HAE medicines – both new and more "mature" products. The HAEi Team (including our Regional Patient Advocates) are ready to take the fight to an even higher level!

With warmest regards to all,

Anthony J. Castaldo
*President, HAEi*


## HAEi Regional Patient Advocates





News from

# The Regional Patient Advocates

**Earlier this year HAEi appointed the first five Regional Patient Advocates, dividing a large portion of the world between them. For the first six months the role of the Regional Patient Advocates is primarily to support the member organizations already in place – after that they will try and help set up more or less formal groups in countries where no organization exists yet.**

The following is an extract from the first reports from some of the Regional Patient Advocates.

### Alejandra Menendez, Latin America

During the HAE Global Conference 2016 I had the opportunity to get together with patient representatives from Brazil, Chile, Colombia, Ecuador, Peru, Mexico, and Venezuela to discuss HAEi's plans for the region. Given the absence of medications and the tremendous interest that the HAE Global Access Program (GAP) has generated for these patients we set up an informal round table discussion with HAEi Project Manager Deborah Corcoran to inform them about the program and try to answer some of the questions they had about it. Representatives from Venezuela made a point they had already begun to work with their physician regarding access to Ruconest through the GAP, however the current political, social and economic situation in the country will likely hinder any kind of progress regarding this possibility. We urged patients' representatives to inform their doctors about the program and Deborah offered advice and help from HAEi.

In June I had an initial official communication as Regional Patient Advocate to representatives from Brazil, Costa Rica, Chile, Colombia, Ecuador, Mexico, Peru, Uruguay, and Venezuela, providing them with specific information on HAEi's plans for the region.

Lately there has also been communication with representatives from Ecuador, Costa Rica, and Cuba:

- In Ecuador there are a number of probable patients who need to be diagnosed, however tests are only done in private practices, which cost approximately 150 USD each. This is considered a huge drawback, since most patients lack the financial means to cover such expenses.
- So far 15 patients have been diagnosed in Costa Rica. There are no medications available and there is very little knowledge about the condition. However, there is a very motivated physician who is caring for HAE patients and is very committed to helping with access to medications. Patients have started presentations to health authorities requesting the importation of current approved treatments, but this is not likely to happen until a robust patient organization pushes for it. So far there is only a patient group, not a formal organization.
- A very motivated physician in Cuba currently serves a small family of HAE patients and is very willing to get in touch with other physicians. Given the social and economic situation in the country, most patients do not have access to Internet so all contact has come solely from the part of the physician.

Among the planned activities are enhanced communication with Brazil, Chile, Colombia, Costa Rica, Venezuela, Uruguay, Peru, and Ecuador to learn about their different health systems. Also, I expect to be reaching out to Mexico and Panama as well as to Cuba and Guatemala.

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### Maria Ferron, Mediterranean Europe

At the HAE Global Conference I was in contact with representatives from France and Italy regarding the current situation in their countries. We also discussed how to approach some of the North African countries, not least Morocco and Algeria. Furthermore, there has been communication with Greece and Cyprus in order to understand the difficulties these countries are facing.

For France the main issue is the lack of information in some areas of the country and some doctors being reluctant to provide home treatment for economical/administrative reasons. In the case of Greece and Cyprus the main issues are the patients' denial and their lack of involvement. When it comes to Portugal patients do not have access to home treatment but there is contact with the Secretary of Health in order to push Icatibant for treatment at home. Finally, in Spain the main issue is the lack of information in some areas and the fact that some doctors are reluctant when it comes to providing home treatment for economical/administrative reasons. HAE Spain (AEDAF) is trying to fight back organizing workshops and three are planned until the end of 2016.

Over the coming months I will be working on a contact to Algeria and keep looking for more contact around North African countries. Other countries on the to-do-list are Monaco, Gibraltar, Andorra, Malta, and Israel.

### Natasa Angjeleska, South East Europe/ Balkans

The HAE Global Conference was an excellent opportunity to meet and exchange info with representatives from Serbia, Greece, Romania, and Turkey.

17-19 June 2016 HAE Macedonia initiated and hosted the first HAEi Balkan Region Meeting for patients and doctors held in Skopje – please see my article on the meeting later in this newsletter.

After the official close out of the meeting, representatives from Turkey requested a short meeting with HAEi Executive Director Henrik Balle Boysen and myself in order to discuss some of their planned activities. Among other things they plan to organize educative school across the country for medical personnel, but they feel that a one day meeting for patients will assist in improved understanding among them, and maybe increased motivation to advocate for themselves.

Recently I have continued the communication with the participants in the Balkan Region Meeting. For instance, I am supporting the patients from Croatia in their work with a physician in developing an HAE information brochure for emergency rooms. Also, I will be continuing the communication with the respective regulatory bodies in Macedonia in order to increase the available vials for patients, enable patients to receive therapy in their town of residence, and have home-treatment. Later on in the fall I expect to target Serbia, Romania, and Slovenia to plan activities and then check up on Albania, Kosovo, and Bosnia-Herzegovina with regard to establishing patient contact.

**Meet them!**

Meet the five Regional Patient Advocates here:

http://haei.org/organization/meet-the-rpas





# 2016 HAEi Balkan Region Meeting

**HAE Macedonia initiated and hosted the first HAEi Balkan Region Meeting for patients and doctors held in Skopje 17-19 June 2016. Natasa Angjeleska, who is the HAEi Regional Patient Advocate for South East Europe/Balkans, has sent this report.**


Being vocal and implementing plenty of activities, patients in Macedonia have made some steps forward in regard to available therapy for HAE. However, there are many obstacles and challenges that need to be overcome and we thought that it would be better if we shared our positive and negative experience with our friends and fellow compatriots in countries from South East Europe.

There were many situations in which we heard authorities find excuses on the results in the procedures for registering and getting available therapy with the fact that we are a small number of patients, small countries etc. We had in mind that the idea about the opportunities to secure therapy in the countries in the region might be more 'attractive' to the pharmaceutical companies to register medicines or make them available through clinical trials and/or donations.

Starting in the autumn 2015, HAE Macedonia representatives had intense communication and used different tools in identifying potential participants (Facebook, e-mail, phone calls etc.) and at the end we had confirmed participation from patients and/or physicians from the host country Macedonia as well as Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Montenegro, Romania, Slovenia, Serbia and Turkey. At the end a total of 44 representatives from 11 countries (Macedonia 7, Serbia 4, Croatia 5, Slovenia 3, Turkey 5, Montenegro 4, Bulgaria 5, Bosnia and Hercegovina 1, Albania 1, and Romania 1 as well as two doctors on specialization studies from Kosovo), President Anthony J. Castaldo and Executive Director Henrik Balle Boysen of HAEi, and the two lecture doctors Bruce Zuraw and Sandra Christiansen from the US HAEA Angioedema Center. Also, one representative from Pharming (Paul Janssen) and one from SOBI (Aleksandra Goshev) were able to participate, which exceeded our expectations. It also signaled great interest among the HAE community in this idea, both among patients and physicians. We didn't have representatives from Greece – they did show interest but they couldn't postpone their obligations in the same period as the dates of the Balkan meeting.

The meeting was very interesting for media representatives from three national TV channels that covered the event in the prime time of the evening news with interviews given by the HAEi President as well as the representatives from HAE Macedonia, Verce Jovanovska Jankovska and myself. Information about the meeting was also announced on several on-line media.

The meeting started with the official program on 18 June with the opening and welcome remarks by the President of HAEi, Anthony J. Castaldo, and the President of HAE Macedonia, Natasa Jovanovska Popovska. HAEi assisted us in having Dr. Zuraw and Dr. Christiansen as main speakers and presenters at the meeting and all of the participants were thrilled to be able to hear their presentations about 'Overview of HAE: The Science, Pathophysiology, Diagnosis, Treatments (Current and Future), and Research'. Their presentation, together with a Q&A session, took almost 2.5 hours and we could feel that our participants were closely following the excellent informative presentations, and were amazed with the immediacy and openness for discussion by

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our guest presenters from the US HAEA Angioedema Center. The agenda for the first day continued with the presentations by Dr. Rijavec from Golnik Klinik in Slovenia in which genetic testing of patients from the region has been made. The afternoon was dedicated to hearing about the country reports presented either by doctors or patients. Each country was requested to prepare a presentation about key HAE aspects, so we heard these presentations:

- Verce Jovanovska Jankovska, HAE in Macedonia (patient representative)
- Dr. Mehmet Hoxha, HAE in Albania (medical representative)
- Konstantin Tzvetkov, HAE in Bulgaria (patient representative)
- Dr. Mensuda Hasanhodžić, HAE in Bosnia and Herzegovina (medical representative)
- Dr. Ljerka Karadzalapic, HAE in Croatia (medical representative)
- Cejovic Vladimir, HAE in Montenegro (patient representative)
- Dr. Noemi-Anna Bara, HAE in Romania (medical representative)
- Ivana Golubovic, HAE in Serbia (patient representative)
- Teja Iskra, HAE in Slovenia (patient representative)
- Ersan Sevinç, HAE in Turkey (patient representative)



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All of the presenters prepared very informative and interesting presentations that assisted us to provide HAEi with relevant information about HAE patients, patient organizations, physicians, care centers, available therapy, and medications for HAE in the respective countries. This information will serve for planning, initiating and implementing future support and activities for these countries by the HAEi Regional Patient Advocate.

Although planned within the agenda on Saturday morning, dr. Aspazija Sofijanova, the President of the Rare Disease Committee in Macedonia, had an emergency situation in the children hospital, where she is a director. However, Dr. Sofijanova came during the organized dinner with the meeting participants and expressed her support for HAE Macedonia activities and her readiness to assist HAE patients in Macedonia within her mandate both as director of the hospital, in which children patients are receiving therapy and care, and as President of the Rare Disease Committee in which she can support and help us advocate for improved treatment for all HAE patients.

The agenda for the next day of the meeting included presentations given by Anthony J. Castaldo and Henrik Balle Boysen about advocating for HAE by patients, as well as opportunities given by the Global Access Program (GAP) for countries in which there is no registered modern HAE medication. Before closing out the meeting a short training session was delivered to the participants by myself with assistance of Verce Jovanovska Jankovska, Vice-President of HAE Macedonia. The aim of this session was to provoke patients to organize themselves and jointly plan actions with assistance of their doctors in order to improve diagnosis, treatment and quality of life in their respective countries after they return.

The meeting was realized in a very positive atmosphere with a lot of communication, exchange of ideas, and plans for future activities in each of the countries. The general conclusions from the meeting are that it will serve as motivation and inspiration for patients to organize activities and seek options for improved diagnosis, treatment and quality of life. All participants were able to realize the importance of self-advocacy and support from good physicians in order to get support from the government.

Almost 900 HAE patients in these countries are identified and registered so far, but assumptions are that there are probably many more. Generally people in this region are in some cases in denial about the illness, as a result of the tradition and culture, and in some cases because there is no information about the possibilities for diagnosis and treatment, patients are not aware about having the disease. There are serious numbers of deaths as a result of late diagnosis, no diagnosis or no treatment available. Modern therapies are treated as luxury, not as a need and patients have limited access to them (only in one hospital or only for throat or abdominal attacks), and it is 'normal situations' for patients to receive fresh frozen plasma and androgens.

There is need for support and additional meetings and communication with the participants so that they can plan activities to improve lives. HAE Macedonia and HAEi expressed their readiness to share ideas, information and offer support in the future.

# Let HAEi host your website

**A growing number of national HAE organizations have their own websites with their own individual hosting solution. However, some of them would like to change hosting or altogether change the look and content of their websites. And others would like to just have a website at all.**

- In order to accommodate any such national HAE organization we have established a system under the HAEi website allowing us to host national websites as well as provide them with templates for an individualized website – naturally all in their native language, says HAEi Executive Director, Henrik Balle Boysen.

At this point national websites have been launched for Iceland, Greece, Kenya, Macedonia, Serbia, Spain, and Turkey – and HAEi is preparing a few more at the moment.

At www.haei.org/haei_countries you'll find an overview of all 52 countries registered with HAEi.

Link to national website hosted by HAEi

Link to national website

– and the national flags on the page link to the HAEi information on the specific country (national organization, care centers, hospitals, available medication etc.).






# HAE News from Around the Globe

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

**Patient Meeting:** HAE Australasia has decided to hold patient meetings bi-annually, continuing to host state and regional meet-ups throughout the year. The next patient meeting will take place in May 2017 in Melbourne.

**Chris Basten Workshops:** HAE Australasia held their first psychology workshops lead by Dr. Chris Basten on 18 June 2016 in Sydney. Patients from Sydney, Canberra and Queensland attended, and two workshops were held, one for adolescents, and one for adults. The workshops were a great success, patients said they felt more connected with others, and afterwards noted that they felt better equipped to keep living with HAE. The group discussions were unstructured and free flowing, and there was enough time to talk about relevant issues. The patients and carers who attended were glad they took the time to attend as they found it useful to discuss how hard things can get with people who know what they are going through. The workshops ensured positive outcomes, and they also found that talking about issues instead of just being given information was useful. The next workshops with Chris Basten are being held alongside a patient meet-up in Brisbane 17 September 2016.

**HAE Global Walk:** In Perth, nine adults, five children and three prams enjoyed a nice walk along the beach while racking up a total of 65,856 steps to add to the tally of the HAE Global Walk organized by HAEi. In New Zealand, there were stunning views of Auckland from the top of One Tree Hill in Cornwall Park, with over 66,000 steps to add to the tally – plus a few thousand dog paw prints.

**Walking the Camino:** Sandra Eriksen from New Zealand was among the 80+ people who took part in the HAEi/ AEDAF Camino Walk leading up to the HAE Global Conference in Madrid in May 2016. Here is her report on the walk as well as the conference:

"Buen camino! Good walk – or enjoy the journey – that's how everyone greets each other on Spain's historic Camino de Santiago. And we had the privilege of joining 80 others from the global HAE community on a three-day walk that took us through beautiful countryside to the magnificent cathedral at Santiago de Compostela, where pilgrims have trekked for centuries.


Our walk proved that people suffering from a debilitating illness can achieve their goals. It was a wonderful way to start our experience of the 2016 HAE Global Conference hosted by Spain in May. Not only did it give us a taste of Galicia's lush rural lifestyle, it was a chance to form special bonds with HAE families from around the world. As we travelled by bus from Madrid we shared stories of how people coped with attacks, the latest treatments, and the help provided by health authorities – or in many cases, the appalling lack of help.

On the walk, as we left behind jetlag, tramped up and down hills, crossed rivers and developed a few blisters and sore muscles, there was the chance to walk and talk with our new friends, or just walk alone at our own pace and enjoy the ambience.

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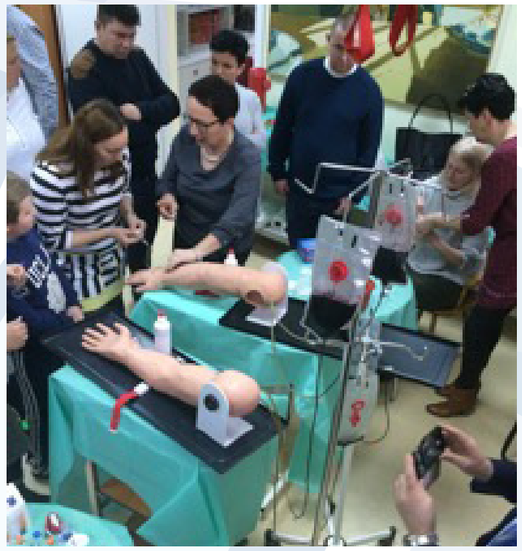
On the third day, after walking into the city of Santiago and marveling at the huge cathedral said to house the ashes of St James (Santiago) we were invited to a special ceremony hosted by the Galician minister of health, which was covered by the local media. The next day, we went by bus to Fisterra, on the wild Atlantic coast, where many pilgrims go on to finish the walk.

By the time we returned to Madrid to join the rest of the 550 delegates for the HAE conference, we had close connections and a special shared experience. We'd heard first hand from fellow walkers from Venezuela, for example, how difficult and expensive it was for them to access essential treatment. I was particularly keen to learn how the HAEi Global Access Program was gearing up to help more patients in countries where there was no government assistance.

Other highlights were hearing about the latest research in San Diego and in Europe, the medical experts panel, and screening of 'Special Blood', a documentary made by Californian patient Natalie Metzger funded by HAEi.

We were also treated to a dramatic flamenco performance, a formal dinner and disco, and a tour of Madrid. All up, a truly informative and great experience – roll on the next HAE global gathering."



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

**Regional Workshop**: 15-16 October the 2016 HAEi CEEC Workshop will take place in Warsaw. The workshop coordinated by HAE Poland will also serve as the Polish national conference. The two day long workshop is expected to gather 130 attendees, including patients, relatives, physicians, nurses, and representatives from the pharmaceutical industry. There will be representation from many of the CEE countries at the workshop..

**Regional patient meetings:** Recently HAE Poland has received confirmation of financial support for four regional HAE patients meetings that will be organized towards the end of 2016. Since November last year, HAE Poland has already organized four regional meetings, taking place in Warszawa, Poznan, Bydgoszcz, and Krakow. There were almost 90 attendees for these meetings, which were organized in hospitals, where HAE Poland helps creating regional HAE centers. This project is developing nicely and great successes have been already seen.

The upcoming meetings are planned to take place in Rzeszow, Bialystok, Wroclaw, and Szczecin, which is no coincidence, as this four cities are located closed to the borders of Belarus, Ukraine, Czech Republic, and Germany – and the aim of the Polish organization is to set up international regional meetings with self-administration courses in order to integrate patients from these countries as some of them live really close to each others.

In cooperation with HAE Belorussia the Polish organization has set up a meeting with Polish physicians in Bialystok for 17 September 2016 – the dates for the other three meetings will follow soon.

**New website:** HAE Poland is working on a new website, hosted under the HAEi umbrella. Hopefully it will be ready for the national conference in October 2016.

**Official recognition**: Through the years HAE has been recognized as a rare genetic disorder, not least among allergologists. That has to do with the fact that Prof. Obtulowicz, often referred to as the God Mother of all polish HAE patients, is an allergologist. This has led HAE Poland to lobby for official recognition with the Polish Society of Allergology and recently this organization has approved the creation of an independent section focused only on HAE. As for now the section contains 25 physicians all around the Poland, now working together on creating official indications to treating the disease as well as the establishment of regional HAE centers in Poland. That is absolutely a great achievement, and HAE Poland is looking forward to working with the HAE section of the Polish Society of Allergology.





**Puerto Rico** **www.facebook.com/haeapr**

**First official meeting:** Earlier this year about 70 patients and family members met in what was the first official gathering of HAE Puerto Rico.

**HAE in Motion:** The US HAEA – working closely with the fellow Americans on the island to identify and organize the local patient community, raise HAE awareness, and dramatically improve access to modern HAE therapies – helped organize a HAE in Motion 5k run/walk at el Parque Central in San Juan on 10 July, where nearly 300 runners enjoyed a sun-filled day and a brunch provided for patients after the event finished.

**Annual meeting:** The first annual meeting of HAE Puerto Rico took place 7 August 2016.

**United Kingdom** **www.haeuk.org**

**From Laura Szutowicz, the CEO of HAE UK:** We have had some excellent news in the last couple of months. Firstly, the Immunology and Allergy Clinical Reference group has elected Dr. Siraj Misbah to be the chairman of the group. The clinical reference groups (CRG) are responsible for setting and implementing clinical practice for the National Health Service (NHS England). Dr. Misbah is a highly experienced and very well-regarded immunologist who has great experience in HAE. The CRG has made two additions to NHS England policy for HAE. One is to authorize use of Oxandrolone in place of Stanozolol, which was being resisted by some pharmacists who were arguing for patients to go back on Danazol, not regarding that the reason they were on Stanozolol was because they could not tolerate Danazol. But the best news is that the CRG has agreed an additional policy regarding prophylaxis with C1-INH. Commissioners are to allow prophylaxis with C1-INH for patients suffering two or more clinically significant attacks per week. This is a great advance on the original recommendations, which were for on-demand use for acute attacks in adults.

More and more of the members of HAE UK are becoming very publicity aware and do everything they can to raise awareness of HAE, we have even some TV stars in the making. More of that in future editions.

We have been very fortunate to have two more clinicians join our Medical Advisory Panel. Dr. Scott Hackett, Paediatric Immunologist from Heartlands Hospital in Birmingham and Dr. Tariq el-Shanawany, Consultant Immunologist from Cardiff. They will bring even more expertise into our already very expert panel, and we are very grateful to them for agreeing to join.

Our wonderful fundraisers have been out again in force, with Rose Joseph running a coffee morning and cycling to raise money for us. And jewelry maker Shirley Granville, who is Executive Officer Rachel Annals' mother in law, donated all proceeds of her recent jewelry sale to HAE UK. We are also running a competition to design HAE UK Christmas Cards, three sections of under 12, 12-18 and over 18s. The winner of each section will see their card printed and we will then sell them to raise funds.

I have been fortunate enough to represent HAE UK at a number of clinical meetings and am pleased that the message coming from doctors and nurses alike is 'do not delay! Use your C1-INH or Icatibant as soon as you think an attack is happening'. We also try to make our members feel empowered to make the decision to treat sooner rather than wait-and-see.

The theme of this year's Patient Day in Bristol is 'Empowerment' and as a reminder, we have set dates and venues for the Patient Day meetings; a Scottish meeting in Perth on 1 October 2016 for all those Scottish patients who tend to be unable to come to the patient day because of distance. Annual Patient Day is 19 November 2016 in Bristol and we are delighted that both Anthony J. Castaldo and Henrik Balle Boysen of HAEi will be attending.

**Austria** **www.hae-austria.at**

HAE Austria celebrated the 10th anniversary of the national organization 3-4 September 2016. We will get back to this in the next newsletter.

**Canada** **www.haecanada.org**

**Upcoming meetings:** The next patient meetings will be held in Winnipeg and Victoria. Information on dates and venues will be posted on the HAE Canada website.

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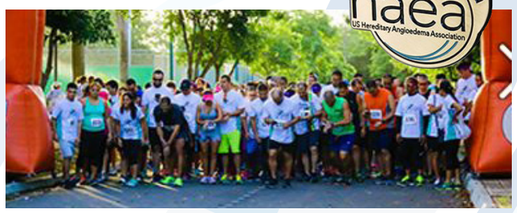
**USA** **www.haea.org**



**HAE in Motion:** US HAEA has created the program 'HAE in Motion', helping patients to arrange 5k walk/ run races in their own communities with full support from the organization. Each year, these events will grow in number and in the impact they have to raise HAE awareness across the US. At the moment these events are scheduled:

- Cincinnati – 10 September 2016
- Rhode Island – October 2016
- Atlanta – 22 October 2016
- San Diego – 6 November 2016
- Florida – November 2016


Each event is created by an HAE patient with the help of the US HAEA and funds raised at all events will go toward research for a cure and the support of patient initiatives. Read much more at http://5k.haea.org.

**Camino Walk:** More than a dozen HAEA members participated in the HAEi/AEDAF Camino Walk for awareness in Spain 14-17 May 2016.

**Global Conference:** US HAEA was proud to be included among the patient group presenters at May's HAE Global Conference in Madrid, Spain. The conference was filled with important information for the 40+ attendees from the US and the organization looks forward to 2018.



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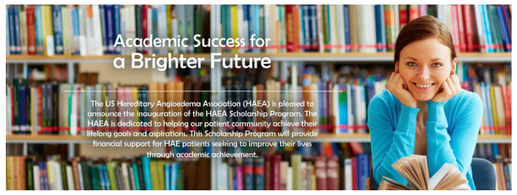
**Going to the Hill:** In June the HAEA took 21 participants to Capitol Hill in Washington, DC to meet with congressional leaders there. The organization advocated for action on political issues that benefit HAE patients in the US. Constituents made their voices heard in over 35 Senate and House offices. Awards were presented to key congressional leaders who have supported the HAEA's efforts.




**Scolarships:** US HAEA provided 30 scholarships to HAE patients headed to college in the fall – congratulations to all of the award recipients. The organization continues to work to help patients of all ages achieve lifelong health.

**Newsletter from the Angioedema Center:** The first US HAEA Angioedema Center newsletter was recently sent to all members of the US organization, containing updates on clincial trials, Question of the Week highlights, as well as news from the center. Have a look at http://bit.ly/29PoyIc.

**South Africa** **www.haei.org/location/hae-in-south-africa**

HAEi is very happy to inform you that the global organization now counts 53 members: In August South Africa was added to the list as Adrienne de Jongh has agreed to be the HAEi representative.

According to Ms. de Jongh South Africa has no access to modern medication. The only product on the market is Danazol and "anything else has to be specially imported along with all the legal nonsense and it also takes forever. In addition to that we do not have a national health system so if you are not destitute you have to fund everything yourself or through a private medical aid which also has its limits. And now that medications are actually becoming available, medical practitioners are not willing to take the risk treating HAE patients without them. Catch 22! A single dose of Berinert costs three times as much as my part time job was paying me per month!"

# Are you ready for the 2017 Camino Walk?

**After the very successful HAEi/AEDAF Camino Walk on the legendary Camino de Santiago in northwestern Spain during the days leading up to the HAE Global Conference 2016 in Madrid, quite a number of people have expressed an interest in repeating the experience in May next year.**

**Consequently HAEi has decided to go ahead and try to organize a Camino Walk to commemorate the global awareness day for HAE haeday :-) in 2017.**

The 2016 HAEi/AEDAF Camino Walk team – that is the President of HAE Spain (AEDAF) Sarah Smith, the HAEi Executive Director Henrik Balle Boysen, the HAEi Communications Manager Steen Bjerre, and the excellent organizer and guide of the 2016 Camino Walk Rafael Moreno – has gladly agreed to organize and support another walk.

- If a sufficient number of people sign up to fill one bus – or more – we will follow the well-known format: departure by bus from Madrid on Saturday 13 May, three days of walking with 15 to 20 kilometers per day on average, and return to Madrid on Wednesday 17 May. The third day of walking, when we would arrive at Santiago de Compostela and the Plaza del Obradoiro, would appropriately coincide with **haeday :-)** in 2017. Returning to Madrid on 17 May we would give the people who plan to attend the 10th C1 Deficiency Workshop in Budapest plenty of time to go there for the beginning of the event, says Sarah Smith.

However, to organize another Camino Walk, HAEi really needs to have fairly soon a reliable estimate of the number of people who would be participating.

- Therefore, we ask anyone interested to contact his or her national organization to find out how many people would be interested in going. Right now we are not asking for a formal commitment or registration, but we would like to know how many people are reliably serious about taking part in this event, says Sarah Smith.

When considering taking part in the 2017 Camino Walk please bear in mind that:

- There will no HAEi travel grants to/from Spain
- The price could be more or less the same as this year (200 EUR per person in shared double room/295 EUR per person in single room), but it may very well be more expensive
- There probably will not be as much leeway to accommodate people who cannot or do not want to do all the walking, i.e. most likely there will be no "Plan B" except for emergencies.

## INTERESTED IN TAKING PART?

The organizers would like to receive information from anyone interested in taking part in the 2017 Camino Walk no later than 14 October 2016. Please reply to

Steen Bjerre at s.bjerre@haei.org or

Sarah Smith at s.smith.foltz@haei.org.



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# Ask the Doctors

**In 2015 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. Below, Dr. Sandra Christiansen, Dr. Marc Riedl, and Dr. Bruce Zuraw answer a recently asked question.**

*"How do I persuade my partner to treat early with C1 inhibitor in case of abdominal pain? I know it is a HAE symptom but he always wants to wait and see."*

**Dr. Christiansen:** This is a deceptively simple question. It is difficult to provide a precise answer lacking some additional background information. How often is your partner correct to wait? Are there certain symptoms that predictable for an HAE attack? Are there other confounding health conditions? How do we convince a loved one to do anything even if it involves their best interest? Facts are often a helpful starting point. As we have emphasized before in discussions of treatment the medications that we have are effective in arresting the attack of swelling. They do not accelerate the resolution. This translates into the longer fluid is leaking out the longer it will take for an attack to resolve. With abdominal attacks delayed treatment equals more pain and misery for the patient. This is compounded by disruption of the attack in every other sector of their life such as work, school or recreation. The other concern is what are the barriers for using the C1 inhibitor? Does your partner not feel comfortable infusing? Are they worried whether they will be able to get sufficient amounts of the drug to have on hand if they have more severe or life threatening symptoms? Have they been made to feel guilty over using such an expensive medication? I would encourage you to have your partner discuss their treatment plan with an HAE specialist who would be equipped to address these issues.

**Dr. Zuraw:** Once the swelling starts, treat as soon as possible. I'll venture into an area, however, where some physicians do have a disagreement. This relates to whether to treat when you are experiencing a prodrome rather than an actual attack. As much as we encourage patients to treat early in an attack, I'm very reluctant to give treatment during a prodrome. Most prodromal symptoms are relatively nonspecific and we don't have information about the probability that the symptom will be followed by an attack. People remember when a symptom was followed by an attack, but they don't remember the times they experienced a transient symptom that was not followed by an attack. Having said that, we recognize that there are always exceptions. If a patient experiences a prodromal symptom that she/he knows with complete certainty will lead to an attack (such as erythema marginatum in some patients), then a good argument can be made for treating at the time of the symptom.



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**Dr. Riedl:** Treating HAE attacks early with effective medication is one of the most important steps in optimizing the acute treatment plan. I hear from patients that abdominal attacks are usually the most difficult to judge, as early on, it can sometimes be difficult to tell whether mild abdominal discomfort is the early stages of angioedema or some other condition such as acid reflux or an upset stomach from a meal. There's many possible causes for abdominal symptoms, making this more difficult to judge compared to skin swelling or airway symptoms. That challenge recognized, we have good clinical studies showing the clear benefit of treating HAE attacks early – the earlier we treat, the faster people get better, and the less time suffered with angioedema symptoms. So while it's quite important and 'easy' to recommend treatment early in an attack, the difficult part is for each person with HAE to be in tune with her/his body and symptoms such that they can best judge when an angioedema attack is starting. As soon as one strongly suspects the symptoms are HAE, that's the time to treat with medication. Waiting to see how severe any attack might get will often lead to problems – once the attack becomes advanced, the medications are unlikely to work as quickly leading to hours or more of debilitating symptoms. The other point I'd emphasize is that IF abdominal pain and symptoms DON'T respond to the FDA-approved HAE medications, then it's very important to get evaluated at the hospital. The modern acute HAE medications are so effective, that if they don't provide relief, then we need to be concerned that some other non-HAE process is occurring. Every once in awhile, other serious intra-abdominal medical problems occur – appendicitis, gall bladder issues, pancreatitis, etc. – and we don't want to miss those things. It's important to avoid 'tunnel vision' whereby we attribute any and all issues to HAE. We become most concerned about these other conditions when symptoms are resistant to the early use of HAE-specific medications.

# Upcoming HAEi Activities

**12-18 September:** HAEi will take part in the annual meeting of Australasian Society of Clinical Immunology and Allergy (ASCIA) at ***Goldcoast, Australia***. ASCIA offers a great opportunity to meet with physicians from all over the Asian continent.

**18-21 September:** HAEi will participate in the Third HAWK Consensus Conference in ***Gargnano, Italy***.

**20-22 September:** HAEi will take part in the Bradykinin Symposium in ***Berlin, Germany***.

**28-30 September:** HAEi will participate in a conference that includes allergist/dermatologist specialists from Southeast Asia. The meeting, taking place in ***Bangkok, Thailand***, will prominently feature HAE and will include a session with patients. We hope this meeting leads to establishing a patient group in Thailand.

# Clinical Trials

**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 should be recruiting at this moment:**

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

Recruiting in United States.

https://clinicaltrials.gov/ct2/show/NCT01832896?term=hereditary+angioedema&recr=Open&rank=1

**Study to Assess the Tolerability and Safety of Ecallantide in Children and Adolescents with HAE – recruiting in United States.**

https://clinicaltrials.gov/ct2/show/NCT01832896?term=hereditary+angioedema&recr=Open&rank=1

**C1 Inhibitor Registry in the Treatment of HAE Attacks – recruiting in Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Norway, Poland, Slovakia, and Sweden.**

https://clinicaltrials.gov/ct2/show/record/NCT01397864?term=hereditary+angioedema&recr=Open&rank=2

**Safety of Ruconest in 2-13 Year Old HAE Patients – recruiting in Czech Republic, Germany, Israel, Italy, Macedonia, Poland, Romania, and Slovakia.**

https://clinicaltrials.gov/ct2/show?term=hereditary+angioedema&recr=Open&rank=3

**Safety and Efficacy Study of Cinryze for Prevention of Angioedema Attacks in Children Ages 6-11 With HAE – recruiting in United States, Germany, Israel, Italy, Mexico, Romania, and United Kingdom.**

https://clinicaltrials.gov/ct2/show?term=hereditary+angioedema&recr=Open&rank=4

**Study to Evaluate the Clinical Efficacy and Safety of Subcutaneously Administered C1 Esterase Inhibitor for the Prevention of Angioedema Attacks in Adolescents and Adults With HAE – recruiting in United States and Spain.**

https://clinicaltrials.gov/ct2/show?term=hereditary+angioedema&recr=Open&rank=5

**Efficacy and Safety Study of DX-2930 to Prevent Acute Angioedema Attacks in Patients With Type I and Type II HAE – recruiting in United States, Canada, Germany, Puerto Rico, and United Kingdom.**

https://clinicaltrials.gov/ct2/show?term=hereditary+angioedema&recr=Open&rank=7

**Determination of Specific Biomarkers of Acute Attack of Angioedema Within Pediatric Population (BRADYKID) – recruiting in France.**

https://clinicaltrials.gov/ct2/show?term=hereditary+angioedema&recr=Open&rank=8

**Firazyr® Patient Registry Protocol (Icatibant Outcome Survey - IOS) – recruiting in Austria, Brazil, Denmark, France, Germany, Greece, Israel, Italy, Spain, Sweden, and United Kingdom.**

https://clinicaltrials.gov/ct2/show?term=hereditary+angioedema&recr=Open&rank=9

**Phase 1 Study to Assess the Safety, Tolerability, and Pharmacokinetics of Recombinant Human C1 Esterase Inhibitor in Healthy Adult Subjects – recruiting in United States.**

https://clinicaltrials.gov/ct2/show?term=hereditary+angioedema&recr=Open&rank=10



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**Determination of Specific Biomarkers of Angioneurotic Crisis (BIOBRAD) – recruiting in France.**

https://clinicaltrials.gov/ct2/show?term=hereditary+angioedema&recr=Open&rank=12

**Screening Protocol for Genetic Diseases of Mast Cell Homeostasis and Activation – recruiting in United States.**

https://clinicaltrials.gov/ct2/show?term=hereditary+angioedema&recr=Open&rank=13

**Study to determine the efficacy and safety of C1 Esterase Inhibitor liquid for injection compared to placebo in the prevention of angioedema attacks in adolescents and adults with HAE – recruiting in Canada, Germany, Hungary, Israel, Romania, Spain, and United States.**

http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2015-002478-19-ES

**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, European Union, Hungary, Israel, United Kingdom, and United States.**

http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2014-001054-42-GB

**A Phase 3, Multicenter, Randomized, Single-Blind, Dose-Ranging, Crossover Study to Evaluate the Safety and Efficacy of Intravenous Administration of Cinryze® (C1 Esterase Inhibitor [Human]) for the Prevention of Angioedema Attacks in Children 6 to 11 Years of Age with HAE – recruiting in Germany, Mexico, Romania, United Kingdom, and United States.**

http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-002453-29-DE

**Pathophysiological study for autoimmune dysregulation of HAE – recruiting in Japan.**

http://apps.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000010754

**Open-label study to evaluate the safety, and efficacy of recombinant human C1 inhibitor for the treatment of acute attacks in pediatric patients with HAE, from 2 up to and including 13 years of age – recruiting in Germany, Israel, and Italy.**

http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-000987-92-IT

**A randomized, placebo-controlled, double-blind Phase III study of the efficacy and safety of recombinant human C1 inhibitor for the treatment of acute attacks in patients with HAE – recruiting in Italy.**

http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2004-004282-15-IT

# HAE Papers

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

**Tolerability and Effectiveness of 17-alpha -Alkylated Androgen Therapy for Hereditary Angioedema: A Re- examination – by Bruce L. Zuraw, Donna K. Davis, Anthony J. Castaldo, and Sandra C. Christiansen:**

This study examines the effectiveness, safety, and tolerability of androgen therapy. Data for the paper was generated from a US HAE Association (US HAEA) sponsored one time, IRB approved, anonymous, web-based survey of patients who reported a history of physician-diagnosed HAE retrospective. The cross-sectional data collection effort involved 650 subjects—the largest cohort of HAE patients ever reported. The US HAEA administered the survey in 2008, when (1) there was no reliably effective acute treatment available in the United States, and (2) a substantial fraction of patients in the United States were managed on prophylactic regimens of androgens.

The authors acknowledge that there are issues with the patient reporting methodology such as the lack of certainty concerning the correct HAE diagnosis, reporting accuracy, and recall bias. They point out, however, that physician reporting of patient attack data may also be subject to significant accuracy concerns due to (1) incomplete data, and (2) the tendency of patients to underreport attacks to physicians. The large size of the subject population is offered as a factor that mitigates the study's limitations. To further support the validity of their approach, the authors cite how closely their data parallels the retrospective case series assessing androgen benefits and risks published by Professor Bork in 2008.

The authors conclude the study as follows: We show that the effectiveness of androgen prophylactic treatment for HAE is highly variable, and that side effects are very common and dose related. In addition, our results highlight that the side effects experienced by patients using androgens are usually multiple and severe. Our data suggest that physicians should exercise caution before increasing the androgen dose in patients who fail to respond well to low or standard doses (200 mg/day of danazol). In view of the dose-related side effects of androgens, these patients may be better managed using an alternative strategy. Considering the improved benefit and safety of plasma derived C1INH relative to androgens, we suggest that woman and children not be treated with androgens, and that androgen therapy in male patients if considered at all be limited to the lowest effective dose, but not exceeding danazol 200 mg/day (or equivalent). Men who experience side effects from low-dose androgen therapy should be switched to an alternative management program. It is essential that the physician have an informed dialog with any patient about the potential benefits and risks of the treatments before selection of a prophylactic therapy. With the improved safety and efficacy profile of plasma derived C1INH, the availability of effective on-demand treatments, and the promise of new more convenient long- term prophylactic options, the role of androgens in the overall management of HAE will likely continue to decline.



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**HAE Pathophysiology and Underlying Mechanisms – by B.L. Zuraw, and S.C. Christiansen SC, University of California, USA:**

Remarkable progress in understanding the pathophysiology and underlying mechanisms of HAE has led to the development of effective treatment. Progress in three separate areas has catalyzed our understanding of HAE: (1) The recognition that HAE type I and type II result from a deficiency in the plasma level of functional C1 inhibitor has led to a detailed understanding of the SERPING1 mutations responsible for this deficiency as well as the molecular regulation of C1 inhibitor expression and function; (2) The fundamental cause of swelling is enhanced contact system activation leading to increased generation of bradykinin. Substantial progress has been made in defining the parameters regulating bradykinin generation and catabolism as well as the receptors that transduce the biologic effects of kinins; (3) The tissue swelling in HAE primarily involves the function of endothelial cell adherens junctions. This knowledge is driving increased attention to the role of endothelial biology in determining disease activity in HAE. However, large gaps still remain in our knowledge. Important areas that remain poorly understood include the factors that lead to very low plasma functional C1 inhibitor levels, the triggers of contact system activation in HAE, and the role of the bradykinin B1 receptor. The phenotypic variability of HAE has been extensively documented but never understood. Future progress in understanding these mechanisms should provide new means to improve the diagnosis and treatment of HAE. (Clin Rev Allergy Immunol., July 2016)

**The Humanistic, Societal, and Pharmaco-economic Burden of Angioedema – by H. Longhurst, Barts Health NHS Trust London, United Kingdom, and A. Bygum, Odense University Hospital, Denmark:**

Historical factors, including the intermittent nature of the disorder, the lack of awareness of this ultra-rare condition amongst medical personnel, lack of specialist centers, and limited treatment options have contributed to under-diagnosis and under-treatment of the condition. Incorrect treatment of attacks has been common, even when medical help is sought. This has lead to reduced health-seeking behavior and alternative coping strategies, sometimes even denial, in many families, while a minority of HAE-affected patients have become serial emergency room attenders with chronic pain and ongoing requirement for opiate-based painkillers. In the last 10 years, new and effective acute therapies have been made available, some of which have also provided short-term and long-term prophylaxis options, together with a better understanding of older prophylactic drugs. Improved awareness of HAE amongst the general public, family members, and physicians has reduced the long delay in diagnosis and increased the number of patients receiving effective and up-to-date therapies to improve the physical impact of the disorder. Data on the impact of treatment on the psychological outcomes is scarce, but the limited information available suggests that access to specialist advice and treatment leads to psychological as well as physical improvement. HAE also has profound effects on individual and family economic output, directly via absenteeism from school or work and indirectly via lost opportunities. Economic improvements associated with better treatments are offset by the high cost of new acute treatments, resulting in difficult pharmaco-economic calculations. Worldwide, cost considerations present potentially insurmountable barriers to treatment for many patients, depending on the healthcare system in the individual country. (Clin Rev Allergy Immunol., July 2016)

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**Thyroid hormones and complement parameters in hereditary angioedema with C1-inhibitor deficiency – by I. Czaller, Semmelweis University, Hungary, et al.:**

Thyroid hormones control and up-regulate the synthesis of many plasma proteins. Minor variations of the thyroid hormone levels (within the reference range) can influence the function of C1-INH in C1-INH-HAE. Our findings suggest a role for the endocrine system in the pathophysiology of C1-INH-HAE. (Ann Allergy Asthma Immunol., June 2016)

**The case for a national service for primary immune deficiency disorders in New Zealand – by R. Ameratunga et al., Auckland City Hospital, New Zealand:**

We propose that HAE is integrated into a national PID (Primary immune deficiency disorders) service. Ancillary services, including the customized genetic testing service, and research are also essential components of an integrated national PID service. A hub-and-spoke model for a national service for PIDs would result in major cost savings, as well as improved patient care. It would also allow seamless transition from paediatric to adult services. (N Z Med J., June 2016)

**Management of Pregnancy and Delivery in Patients With HAE Due to C1 Inhibitor Deficiency – by T. González-Quevedo, Hospital Universitario V del Rocío, Spain, et al.:**

We reviewed 125 full-term pregnancies (89 without a prior diagnosis of C1INH-HAE), 14 miscarriages, and four induced abortions. Pregnancy has a variable influence on the clinical expression of C1INH-HAE. Attacks tend to occur more frequently but not to increase in severity. Vaginal delivery was mostly well tolerated. pdhC1INH prophylaxis should be administered prior to cesarean delivery and is also recommended before vaginal delivery if there are additional risk factors. pdhC1INH should always be available in the delivery room. (J Investig Allergol Clin Immunol., 2016)

**Allergenicity and safety of recombinant human C1 esterase inhibitor in patients with allergy to rabbit or cow's milk – by M.T. van den Elzen, University Medical Center Utrecht, The Netherlands, et al.:**

Recombinant human C1 inhibitor (rhC1INH) for on-demand treatment of HAE is purified from milk of transgenic rabbits. It contains low amounts (<0.002%) of host-related impurities, which could trigger hypersensitivity reactions in patients with rabbit allergy (RA) and/or cow's milk allergy (CMA). Twenty-six patients with RA and/or CMA were enrolled. None of the patients with negative skin prick test (SPT) and intracutaneous test (ICT) results for rhC1INH had allergic symptoms during rhC1INH challenge. The negative predictive value of the combination of SPT and ICT for the outcome of the subcutaneous challenge was 100% (95% CI, 84.6%-100%). Subcutaneous administration of rhC1INH was well tolerated. (J Allergy Clin Immunol., May 2016)



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**The Story of Angioedema: from Quincke to Bradykinin – by A. Reshef, Sheba Medical Center, Israel, et al.:**

The term 'swelling' has been used in the old scriptures to illustrate a change of normal figure and, as such, an expression of illness. The great Greek physician Hippocrates (377-460 BC), considered one of the most outstanding figures in the history of medicine and 'Father of the Western Medicine', already used the term oídēma to describe swelling of organs. It took many centuries later until the first description of angioedema as a distinct medical entity was minted by Quinke (1882). It took 75 years from the accurate description of HAE by Osler (1888), until a group of researchers headed by Donaldson (1963) disclosed the central role of C1 inhibitor in angioedema pathophysiology. What followed was a result of a collective effort by many researchers and scientific groups who were able to elucidate the intricate connections between the implicated biochemical pathways. Another 45 years had to elapse until the renewed interest in HAE was boosted by studies on the efficacy and safety of novel therapies about 10 years ago. In the twenty-first century, HAE ceased to be an 'orphan disease' and its future is far more optimistic. It is better managed now by specialized angioedema centers, harmonized clinical guidelines, educational programs, laboratory services, and continued basic and clinical research. Patient associations worldwide are offering support and guidance, and governments and healthcare systems are gradually addressing patient and family needs. (Clin Rev Allergy Immunol., June 2016)

**Safety and Usage of C1-Inhibitor in HAE: Berinert Registry Data – by M.A. Riedl, University of California, United States, et al.:**

The plasma-derived, highly purified, nanofiltered C1-inhibitor concentrate (Berinert; "pnfC1-INH") is approved in the United States for treating HAE attacks and in many European countries for attack treatment and short-term prophylaxis. A multicenter, observational, registry was conducted between 2010 and 2014 at 30 United States and seven European sites to obtain both prospective and retrospective safety and usage data on subjects receiving pnfC1-INH for any reason. The findings documented widespread implementation of pnfC1-INH self-administration outside of a health care setting consistent with current HAE guidelines. These real-world data revealed pnfC1-INH usage for a variety of reasons in patients with HAE and showed a high level of safety regardless of administration setting or reason for use. (J Allergy Clin Immunol Pract., June 2016)

**Frequent life-threatening laryngeal attacks in two Croatian families with HAE due to C1 inhibitor deficiency harbouring a novel frameshift mutation in SERPING1 – by L. Karadža-Lapić, General Hospital Šibenik, Croatia, et al.:**

Twenty-three subjects from two families were recruited for clinical data evaluation and molecular analysis. Decreased levels of C1 inhibitor were detected in 12 adult patients and three young asymptomatic persons. The same novel deletion of two nucleotides on exon 3 was identified in all of them. A history of laryngeal oedema was present in 10 patients, and all patients reported laryngeal attacks at least once a year. The delay in diagnosis decreased noticeably from the first to the last generation. We identified a novel causative mutation in SERPING1 in several affected members of two apparently unrelated families with a high frequency of laryngeal oedema. Molecular analysis of large C1-INH-HAE families will provide new insights on the genotype-phenotype relationship. (Ann Med., May 2016)

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**Safety, pharmacokinetics, and pharmacodynamics of avoralstat, an oral plasma kallikrein inhibitor: phase 1 study – by M. Cornpropst, BioCryst Pharmaceuticals, United States, et al.:**

Avoralstat is a potent small-molecule oral plasma kallikrein inhibitor under development for treatment of HAE. This first-in-human study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of avoralstat. Avoralstat was well tolerated, and drug exposure was sufficient to meet target levels for inhibition of plasma kallikrein. Based on these results, the 400 mg q8 h dose was selected for further evaluation in patients with HAE. (Allergy., May 2016)

**Plasmin is a natural trigger for bradykinin production in patients with HAE with factor XII mutations – by S. de Maat, University Medical Center Utrecht, The Netherlands, et al.:**

Patients with angioedema experience unpredictable attacks of tissue swelling in which bradykinin is implicated. Several distinct mutations in Factor XII (FXII) are associated with HAE in the presence of normal C1 esterase inhibitor activity (FXII-HAE). The underlying disease mechanisms are unclear, which complicates diagnosis and treatment. FXII-HAE mutations collectively introduce new sites that are sensitive to enzymatic cleavage by plasmin. These FXII mutants rapidly activate after cleavage by plasmin, escape from inhibition through C1 esterase inhibitor, and elicit excessive bradykinin formation. Furthermore, our findings indicate that plasmin modulates disease activity in patients with FXII-HAE. Finally, we show that soluble lysine analogs attenuate this mechanism, explaining their therapeutic value in patients with HAE. Our findings indicate a new pathway for bradykinin formation in patients with HAE, in which FXII is cleaved and activated by plasmin. This should lead to the identification of new markers for diagnosis and targets for treatment. (J Allergy Clin Immunol., April 2016)

**Bradykinin: Inflammatory Product of the Coagulation System – by Z. Hofman et al., University Medical Center Utrecht, The Netherlands:**

We put forward the paradigm that FXII functions as a 'sensor molecule' to detect conditions that require bradykinin release via crosstalk with cell-derived enzymes. Understanding the mechanisms that drive bradykinin generation may help to identify angioedema patients that have bradykinin-mediated disease and could benefit from a targeted treatment. (Clin Rev Allergy Immunol., April 2016)

**HAE due to C1 - inhibitor deficiency in Switzerland: clinical characteristics and therapeutic modalities within a cohort study – by U.C. Steiner, University Hospital Zurich, Switzerland, et al.:**

Of 135 patients, data from 104 patients (77%) were available for analysis. We found large differences of HAE in male and female both in terms of symptom number and swelling episodes. Women are more affected by intensity and frequency of angioedema episodes than men. Danazol treatment remains widely used as effective prophylaxis despite its side effects. New therapies which selectively influence the hormonal estrogen balance could open new therapeutic options mainly for women and maybe also for men. (Orphanet J Rare Dis., April 2016)

**First report of icatibant treatment in a pregnant patient with HAE – by H. Farkas et al., Semmelweis University, Hungary:**

Plasma-derived nanofiltered C1-INH (pnfC1-INH) is the only recommended therapeutic option during pregnancy. In our 26-year-old female patient with type II C1-INH-HAE, pregnancy was confirmed in the sixth week of gestation. During this period, the patient received the bradykinin B2-receptor antagonist, icatibant, on five occasions, as acute treatment. She experienced 119 attacks, for which she received 108 vials of pnfC1-INH during her pregnancy. The patient gave birth to a healthy baby. No side effects were detected with either treatment. (J Obstet Gynaecol Res., August 2016)



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**Prophylaxis in hereditary angioedema (HAE) with C1 inhibitor deficiency – by J. Greve, Ulm University Medical Center, Germany, et al.:**

Attenuated androgens used to be the drugs of choice, but they are associated with considerable side effects and no longer commercially available in the German-speaking countries of the EU. More effective and more tolerable agents are currently replacing them. These new drugs have had a major impact, especially on the indications and procedures for long-term prophylaxis. According to the most recent international consensus papers and our own experience, self-administered C1-inhibitors are now the first option for long-term prophylactic therapy. The decision for prophylaxis should no longer be based on single parameters such as the frequency of attacks but on adequate overall disease control including quality of life. (J Dtsch Dermatol Ges., March 2016)

**HAE in a Jordanian family with a novel missense mutation in the C1-inhibitor N-terminal domain – by S.A. Jaradat, Jordan University of Science and Technology, Jordan, et al.:**

A Jordanian family, including 14 individuals with C1-INH-HAE clinical symptoms, was studied. In the propositus and his parents, SERPING1 had four mutations leading to amino acid substitutions. Two are known polymorphic variants, the others are newly described. DNA from additional 24 family members were screened. Angioedema symptoms were present in 14 of 16 subjects. This family-based study provides the first evidence that multiple amino acid substitutions in SERPING1 could influence C1-INH-HAE phenotype. (Mol Immunol., March 2016)

# News from the Industry

## PHARMING

**15** July, 2016

**Pharming Group NV** and **Swedish Orphan Biovitrum AB (Sobi)** has signed an amendment of their Ruconest distribution agreement from 2009.

In addition to Austria, Germany and Netherlands, Pharming will market Ruconest directly into an additional 21 countries, effective 1 October 2016. These countries include Algeria, Andorra, Bahrain, Belgium, France, Ireland, Jordan, Kuwait, Lebanon, Luxembourg, Morocco, Oman, Portugal, Qatar, Syria, Spain, Switzerland, Tunisia, United Arab Emirates, United Kingdom, and Yemen.

To support the commercialization, Pharming will expand the current small European team of experienced HAE marketing and medical affairs specialists.

To ensure a seamless hand-over and guarantee the continuous availability of Ruconest to patients, Sobi will continue to deliver Ruconest and continue the drug safety monitoring and reporting, until 1 October 2016.

Sijmen de Vries, Pharming's CEO, commented, "The extension of our direct commercialization of Ruconest into these additional 21 markets is a further step towards our goal of becoming a specialty pharma company with significant commercial infrastructure to be able to fully benefit from the added value of bringing our products to patients. Despite Ruconest sales in these important markets being modest, this move is expected to have a positive impact on our financial performance, as we will be able to improve the margin from sales with every vial of Ruconest sold.

(Source: Pharming)



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## PHARMING

**18** July, 2016

**Pharming Group N.V.** has announced positive results from a Phase 2 clinical study of Ruconest (recombinant C1 esterase inhibitor, 50 IU/kg) for prophylaxis in patients with HAE. In the study, Ruconest showed a clinically relevant and statistically significant reduction in attack frequency for both the twice-weekly and once-weekly treatment regimens as compared with placebo.

32 HAE patients deficient in C1 esterase inhibitor and with a history of at least four attacks per month were enrolled in the randomized, double-blind, placebo-controlled study. The patients received Ruconest once and twice weekly and placebo in each of three four-week treatment periods in a cross-over design. The primary efficacy endpoint was the number of HAE attacks per 28 day treatment period and the secondary endpoint was clinical response, defined as a ≥ 50% reduction in the number of attacks from treatment with placebo to treatment with Ruconest.

In the intent-to-treat analysis (ITT), the study found a statistically significant difference in the mean number of HAE attacks that patients experienced during treatment with both the twice-weekly (p-value <0.0001) and once-weekly (p-value =0.0004) Ruconest regimen as compared with placebo.

Patients on placebo had a mean of 7.2 attacks (95% confidence interval[CI]: 5.8-8.6) per four week treatment period which was reduced to a mean of 2.7 attacks on Ruconest twice weekly (95% CI: 1.8-3.7) and a mean of 4.4 attacks on Ruconest once-weekly (95% CI: 3.1-5.6).

For the analysis of the secondary endpoint in the ITT population, 74% of patients (95% CI: 57-86) on the twice-weekly Ruconest regimen had at least a 50% reduction in their attack frequency.

This was confirmed in the per-protocol population of patients, which included patients who completed the study without any major deviations (n=23), where 96% of patients (95% CI: 79-99) on the twice-weekly Ruconest regimen and 57% (95%CI: 37-74) on the once weekly Ruconest regimen had at least a 50% reduction in their attack frequency. Furthermore, in this group, twice weekly Ruconest treatment reduced the attack frequency by 72% (95% CI: 63-81) and once weekly Ruconest treatment reduced attack frequency by 44% (95% CI: 27-62) as compared with placebo.

Ruconest was generally well-tolerated in the study. No patients withdrew from the study due to adverse events. There were no related serious adverse events. There were no thrombotic or thromboembolic events observed. There were no hypersensitivity or anaphylactic reactions. There were also no neutralizing antibodies detected.

Marc Riedl, Professor of Medicine and Clinical Director of the US HAEA Angioedema Center at UCSD and co-prinicipal investigator for the study, commented: "The results of this well-controlled prophylactic study demonstrate a clinically relevant reduction of HAE attack frequency and a high responder rate with the recombinant C1INH treatment. Combined with the excellent safety profile, this data supports further development of recombinant C1INH as a useful preventive therapy for HAE."

Marco Cicardi, Professor of Internal Medicine University of Milan, Hospital L. Sacco Milan and co-prinicipal investigator for the study, remarked: "The clinical efficacy and responder rate in this well-controlled study clearly indicate that, despite its short half life, recombinant C1-inhibitor has the potential to become a prophylactic treatment for HAE. The results also mark an important step forward to further understanding the underlying mode of action of C1-inhibitor therapy in the treatment of HAE."

Prof. Dr. Bruno Giannetti, Pharming's COO, added: "We are very encouraged by these results and now look forward to reviewing the results with the FDA and EMA to be able to determine how to bring Ruconest, as the first and only recombinant C1- inhibitor, to patients who need prophylactic treatment for their HAE."

Under the terms of the North American licensing agreement with Valeant Pharmaceuticals International, Valeant and Pharming share 50/50 the development costs for Ruconest for prophylaxis of HAE. Pharming will receive an undisclosed milestone payment from Valeant as and when FDA approval for this additional indication is given. Ruconest has been granted Orphan Drug designation by FDA for the prophylactic treatment of angioedema caused by hereditary or acquired C1 esterase inhibitor deficiency, with data exclusivity until 2026 under the Biologics Price Competition and Innovation Act.

(Source: Pharming)

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# CSL Behring

**19** July, 2016

The U.S. Food and Drug Administration (FDA) has approved the use of Berinert [C1 Esterase Inhibitor (Human)], the **CSL Behring** therapy for treating HAE attacks, for use in pediatric patients. This expands the use of Berinert into all age groups, making it the first and only approved HAE treatment available to patients under 12 years of age.

A child has a 50 percent chance of inheriting this disease if one of his or her parents has it. Machelle Pecoraro, HAE patient and HAE caregiver, shares "When your child has been diagnosed with HAE, you have to fight for a better life for them."

"This is an important milestone for children living with HAE and their caregivers, to know that there is a FDA approved, safe and effective treatment option for children," says Bob Repella, Executive Vice President, Commercial Operations, CSL Behring. "This expanded indication is an example of CSL Behring's commitment to HAE and our continuing efforts to deliver on our promise to improve the care of patients living with serious medical conditions."

In addition to the pediatric indication, the FDA approved an update to the Geriatric Use section of the package insert. The safety and efficacy of Berinert have been established in both children and adults, with safety profiles observed in the pediatric and geriatric populations similar to that observed in other populations. Clinical studies have shown that intervention with Berinert at the onset of an HAE attack brings significantly faster relief to a patient and reduces the severity of the attack.

(Source: CSL Behring)

BioCryst Pharmaceuticals, Inc.

**5** Aug, 2016

Announcing the **BioCryst Pharmaceuticals** financial results for the second quarter of 2016 Jon P. Stonehouse, President & CEO, said:

"We continue to make progress, and have initiated subject screening to start the APeX-1 trial evaluating our once daily oral kallikrein inhibitor BCX7353 to prevent HAE attacks. Our goal remains to report out initial data by year end for this trial."

Corporate Update & Outlook:

- The APeX-1 clinical trial of BCX7353 for prophylaxis of angioedema attacks in patients with HAE has received regulatory approval in Canada and several European countries, and patient screening has commenced. We expect initial data from APeX-1 to be available by year end 2016.
- A clinical pharmacology study of several dosage formulations of avoralstat is nearing completion. Cohorts of healthy volunteers have received single doses ranging from 200 mg to 2000 mg of avoralstat in tablet or suspension formulations, with no clinically significant adverse events reported. While these dosing formulations have improved total avoralstat exposure (AUC) up to approximately five-fold compared to a 500 mg dose given as soft gel capsules, the plasma concentration-time profile has not met our objectives of twice-daily dosing with drug levels at or above the target range. For that reason, we have decided to stop further development of avoralstat.
- A phase 1 first-in-human study of the broad-spectrum antiviral drug BCX4430 has been completed. Study drug was administered by i.m. injection to healthy volunteers. Single doses of BCX4430 ranging from 0.3 to 10 mg/kg were administered, and daily doses of 2.5 mg/kg to 10 mg/kg were administered for 7 days. Exposure to BCX4430 was dose-proportional. BCX4430 dosing was generally safe and well-tolerated, and there were no grade 3 or 4 adverse events.
- On July 5, 2016, BioCryst announced that the National Institute of Allergy and Infectious Diseases (NIAID) has provided additional funding for efficacy studies of BCX4430 in non-human primates to further assess effective dose regimens.

(Source: BioCryst)





# PHARMING

**8** Aug, 2016

**Pharming Group N.V.** has entered into a definitive agreement to acquire all North American commercialization rights to its own product Ruconest (recombinant human C1 esterase inhibitor), including all rights in the US, Mexico and Canada, from Valeant Pharmaceuticals International, Inc.

Ruconest is an orphan drug designated therapy developed by Pharming, already approved for the treatment of acute HAE attacks in patients in the USA and EU. This transaction will accelerate Pharming's development into a profitable specialty pharmaceutical company with its own independent commercial infrastructure, which will form the foundation for growth in the future.

To ensure a seamless transition, Pharming is anticipating that Valeant's dedicated Ruconest sales force, a total of 11 people, will accept offers to join Pharming to continue the Ruconest sales effort in the USA. Pharming also plans to increase the size of the sales force to drive growth in product sales, together with increased investments in medical science liaison personnel and additional marketing activities, including patient advocacy programs and the provision of significant unconditional support for the US HAEA and its programs as well as other HAE centers of excellence in the USA. In addition, Pharming is planning further investment in the acceleration of Ruconest sales efforts to drive growth in the EU, Middle East and Africa markets which Pharming will take over in October from SOBI, as announced on 14 July 2016, and to make Ruconest available in Canada and Mexico.

Valeant and Pharming will work closely on the transition for customers and HAE patients under a transition services agreement entered into at the same time as the transaction. This will enable Pharming to replace core functions currently undertaken by Valeant and its contractors in a timely manner.

Sijmen de Vries, Pharming CEO, commented:

"This is a quantum leap forward for Pharming and marks a significant point in the Company taking control of its own destiny and providing a real prospect of reaching profitability soon. In previous years, milestones and revenues from the US license for Ruconest provided funding for the Company's independence as well as the production of Ruconest, thereby enabling the best prospect for HAE patients at the time. Now, we are able to take control of our key asset and make it available to all HAE patients in the US with a single-minded focus, dedication, energy and investment. For over a decade Pharming has been instrumental in the HAE market and has been working with physicians treating HAE and HAE patients for many years on the development of a safe and effective recombinant enzyme replacement therapy for HAE sufferers.

(Source: Pharming)

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**11** Aug, 2016

**BioCryst Pharmaceuticals, Inc.** has dosed the first subject in the APeX-1 clinical trial of BCX7353 for the oral treatment of HAE.

"We are very pleased that the adaptively-designed APeX-1 trial is now under way, and look forward to reporting Part 1 results around the end of 2016," said William P Sheridan, SVP & Chief Medical Officer at BioCryst. "Results of the phase 1 study of '7353 support its potential to provide a normal life to HAE patients as a once-daily oral treatment by increasing kallikrein inhibition to normal levels."

APeX-1 is a two part, Phase 2, randomized, double-blind, placebo-controlled dose ranging trial to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of BCX7353 as a preventative treatment to eliminate or reduce the frequency of angioedema attacks in HAE patients. Up to approximately 50 eligible subjects with HAE will be enrolled in the study.

"The APeX-1 trial is an exciting opportunity for the HAE patient community." said Dr. Emel Aygören-Pürsün, M.D., Head of Angioedema Clinic, Goethe University Hospital Frankfurt/Main Pediatric Clinic, Frankfurt, Germany, and Principal Investigator for APeX-1. "The value of an effective and well tolerated oral preventive treatment for HAE patients cannot be overestimated."

In part 1 of APeX-1, subjects with HAE will be randomized in a 1:1 ratio to receive an oral dose of either 350 mg of BCX7353 once daily or placebo once daily for four weeks. An interim analysis will be conducted after the first 24 subjects have completed treatment through study day 28. If a robust treatment effect is observed at the interim analysis, Part 2 of the study will be initiated. In the event the treatment effect is not well characterized with 24 subjects, a total of up to approximately 36 subjects will be enrolled in part 1. The sample size in Part 1 was kept flexible to cover a range of response options that would achieve 90 % power with an alpha of 0.05, based on reduction of attack rate of at least 70 % on BCX7353, placebo response rate of approximately 30%, and standard deviation of approximately 0.45 attacks per week.

To characterize dose-response in part 2 of APeX-1, 14 additional subjects with HAE will be randomized to 250mg of BCX7353 once daily (n=6), 125mg of BCX7353 once daily (n=6) or placebo (n=2).

The primary efficacy endpoint of APeX-1 is the number of angioedema attacks; attack rate per week, counts of attacks, proportion of subjects with no attacks, and number of attack-free days will be analyzed. Efficacy analyses will be conducted for HAE attacks reported over the entire dosing interval (Days 1 through 28) and during the dosing period in which plasma concentrations of BCX7353 should be at steady-state conditions (Days 8 through 28). Secondary efficacy endpoints include severity and duration of angioedema attacks, and measures of health-related quality of life. Safety will be characterized through evaluation of adverse events and laboratory testing. Pharmacokinetics and pharmacodynamic effects will be assessed through measurement of plasma drug levels and kallikrein inhibition.

Additional details regarding the APeX-1 trial design will be posted to www.clinicaltrials.gov.

Discovered by BioCryst, BCX7353 is a novel, once-daily, selective inhibitor of plasma kallikrein in development for the prevention of angioedema attacks in patients diagnosed with HAE. By inhibiting plasma kallikrein, BCX7353 suppresses bradykinin production. Bradykinin is the mediator of acute swelling attacks in HAE patients. BCX7353 has been generally safe and well tolerated in clinical pharmacology studies that have enrolled 117 healthy volunteers, 46 receiving single doses of up to 1000 mg, and 71 receiving once-daily doses of up to 500 mg for 7 days and 350 mg for 14 days. In the second week of study, approximately 5 % of healthy volunteers administered daily doses of '7353 for at least 7 days developed a drug-related skin rash that resolved within a few days.

(Source: BioCryst)





**11** Aug, 2016

**KalVista Pharmaceuticals** announces the dosing of the first subject in a first-in-human clinical trial to evaluate the safety, pharmacokinetics and pharmacodynamics of orally delivered KVD818 in healthy volunteers. A KalVista discovery, KVD818 is a novel, potent, and selective inhibitor of plasma kallikrein in development for the prevention of attacks of edema in patients with HAE.

Andrew Crockett, KalVista's CEO, said: "The successful dosing of the first subject in this first-in-human clinical trial is an important milestone for the KVD818 development program and a first step in our goal of developing a best in class oral plasma kallikrein inhibitor for HAE. We believe that an oral drug for the treatment of HAE will be an important advancement for patients who suffer from this condition."

This first clinical study will provide data to evaluate the key characteristics of safety, drug exposure and bioactivity (plasma kallikrein inhibition) achieved after oral dosing of KVD818. This clinical trial is being conducted in the United Kingdom and the results of this study are expected to be announced in the first half of 2017. If the Phase 1 program achieves its goals, KalVista plans to initiate a Phase 2 trial in HAE patients.

(Source: KalVista)

# CSL Behring

**30** Aug, 2016

The U.S. Food and Drug Administration (FDA) has accepted for review the Biologics License Application (BLA) for **CSL Behring**'s low-volume subcutaneous (SC) C1-Esterase Inhibitor (C1-INH) Human replacement therapy, CSL830, as prophylaxis to prevent HAE attacks.

"The review of this application is another step towards providing advanced prophylactic treatment options to people living with HAE," said Dr. Andrew Cuthbertson, Chief Scientific Officer and R&D Director, CSL Limited. "Since we first reported the possibility of C1-INH replacement therapy for HAE over 40 years ago, we have remained committed to innovative research and providing advanced treatment options to people living with HAE. Subcutaneous prophylaxis is the next important step in helping HAE patients to prevent HAE attacks."

(Source: CSL Behring)

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 Worldwide

Currently you will find HAE member organizations in 53 countries:

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

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

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

**Europe (28)**: Austria, Belarus, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Macedonia, Norway, Poland, Portugal, Romania, Serbia, Slovenia, Spain, Sweden, Switzerland, The Netherlands, Ukraine, United Kingdom

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

**Africa (2)**: Kenya, South Africa

**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 organizations .

### 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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