White Paper

Harnessing the Power of Patient Organisations: A Case Study of PO-Driven Drug Development in Ultra-Rare Disease

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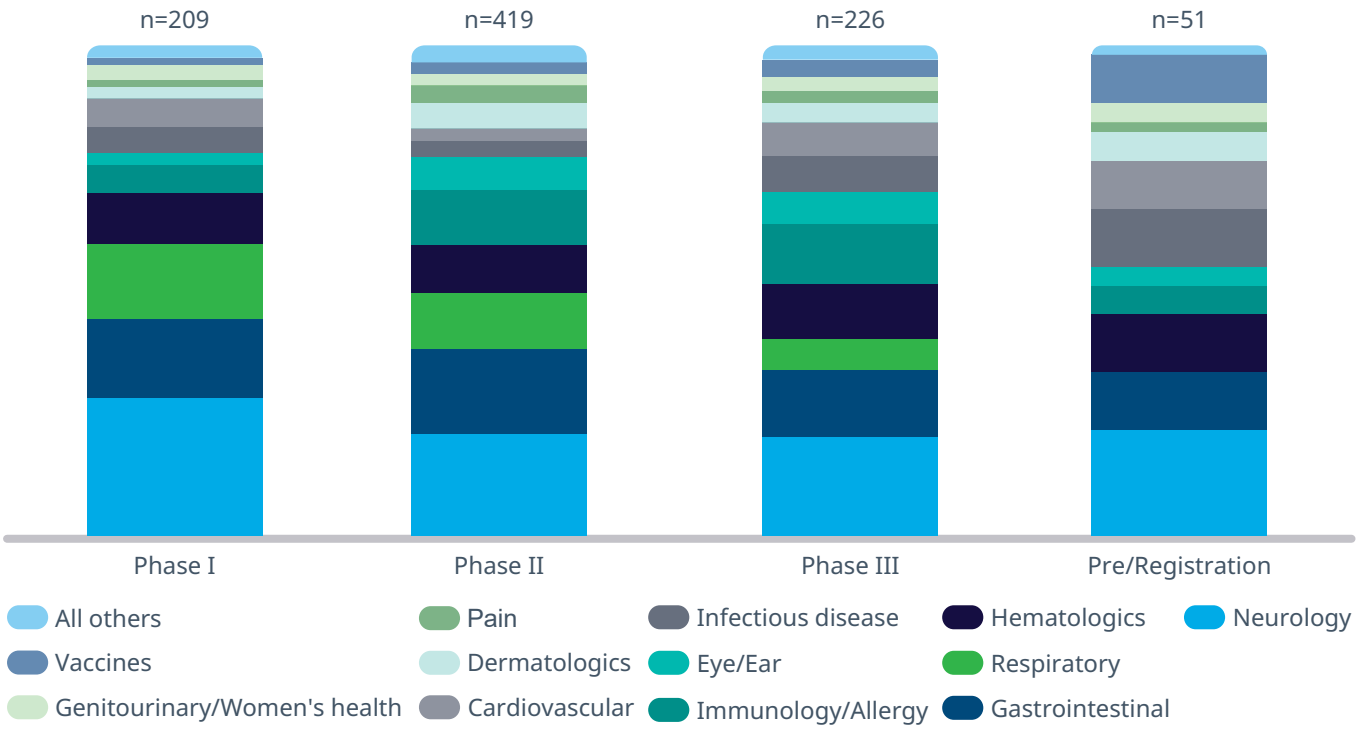
Introduction: The burden of rare diseases

Rare and ultra-rare diseases are characterised simultaneously by great unmet need and significant R&D activity. In the EU, a condition is considered rare if it affects fewer than 5 in 10,000 people. Over 6,000 diseases fall under this definition and 1 in 17, or up to 36 million people, are affected. For most of these diseases, no treatment exists.[1,2]

At the same time, there are currently around 900 molecules being investigated for rare diseases, accounting for about 15% of the entire R&D pipeline.

Figure 1: Rare disease pipeline excluding oncology,
Phase I to regulatory submission, by phase, 2022

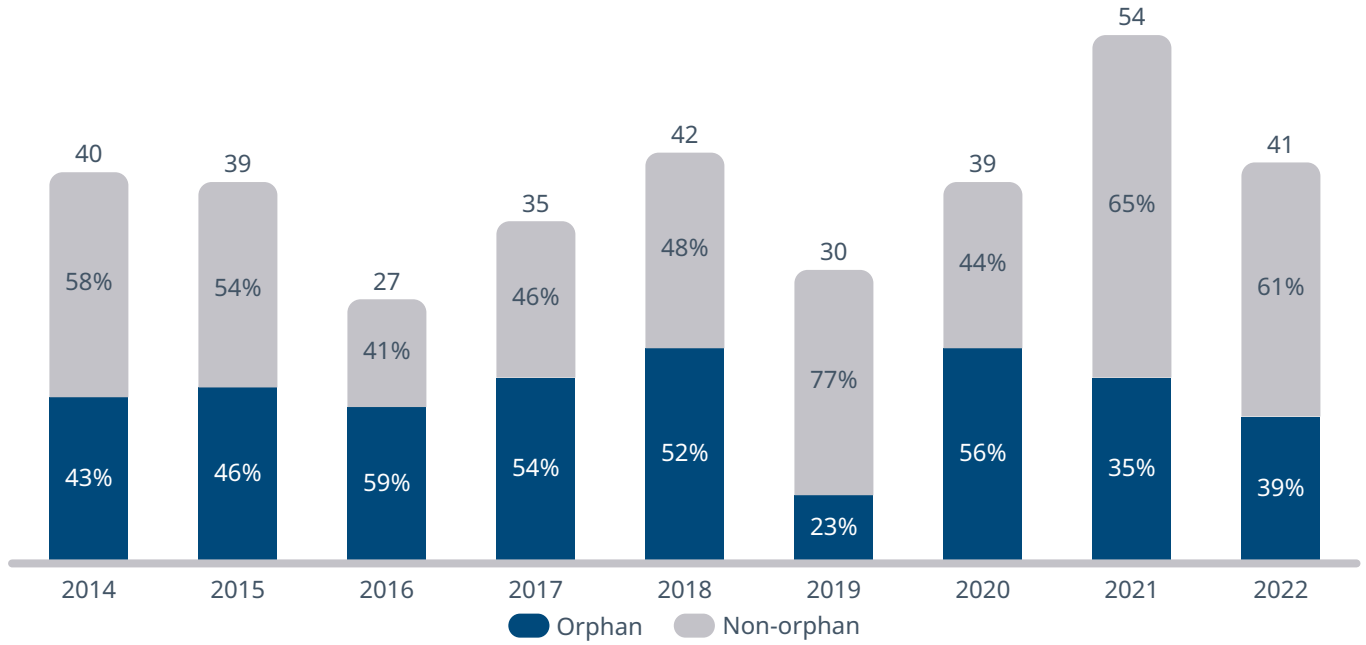


Source: IQVIA Institute, Jan 2023

The challenges of development in rare disease are reflected in variable developmental success rates — in 2022 the composite success rate across all development phases was 7% against 14% in 2021.[3]

However, overall orphan drugs have weathered the difficult post-pandemic launch environment comparatively well[4] and in recent years have made up 40-50% of approvals in the EU.

Figure 2: Orphan vs. non-orphan drug approvals in the EU



Source: IQVIA EMEA Thought Leadership; EMA

Patient identification, recruitment, and retention are crucial for successful drug development, but also particularly challenging in rare diseases because of the already low numbers of trial participants and the often widely dispersed patient populations. While AI-powered solutions can help with the technical task of identifying potential candidates by winnowing through vast amounts of patient data,[5] patient organisations can play a pivotal role in giving valuable input into trial design from the patient viewpoint and in motivating their patient communities to participate in the trials.

In some cases, patient organisations go even further and drive the development of much-needed treatments. One such case is the development of nitisinone as a treatment for Alkaptonuria (AKU), which we present in the following case study.

We thank the AKU Society for generously providing in-depth insights into this seminal project, from which valuable lessons can be drawn for both the pharmaceutical industry and patient organisations.

Developing a treatment for Alkaptonuria (AKU)

What is Alkaptonuria?

Alkaptonuria (AKU) is a rare genetic disease caused by a deficiency in the enzyme homogentisate 1,2-dioxygenase. The accumulation of homogentisic acid (HGA) resulting from this deficiency leads to the formation of an ochronotic pigment, which is deposited in, and ultimately causes damage to, joints and connective tissues such as the eye and cartilage. AKU affects many parts of the body, although its manifestation varies between individuals. It can lead to brittle bones, arthritis, tendon or muscle ruptures, renal or prostatic stones, renal failure, fractures, damage to the cardiovascular system, and other symptoms.

AKU is a slowly progressive disease, and with the exception of dark urine — which often goes unnoticed — symptoms generally don't develop until early adulthood. The prevalence of AKU is typically between 1:250,000 and 1:1,000,000 and is therefore considered an "ultra-rare" disease. Due to both its rarity and its symptoms sometimes resembling other types of arthritis, AKU is frequently misdiagnosed until orthopaedic surgery reveals that the patient's joint displays the distinctive blue-black discolouration.[6,7]

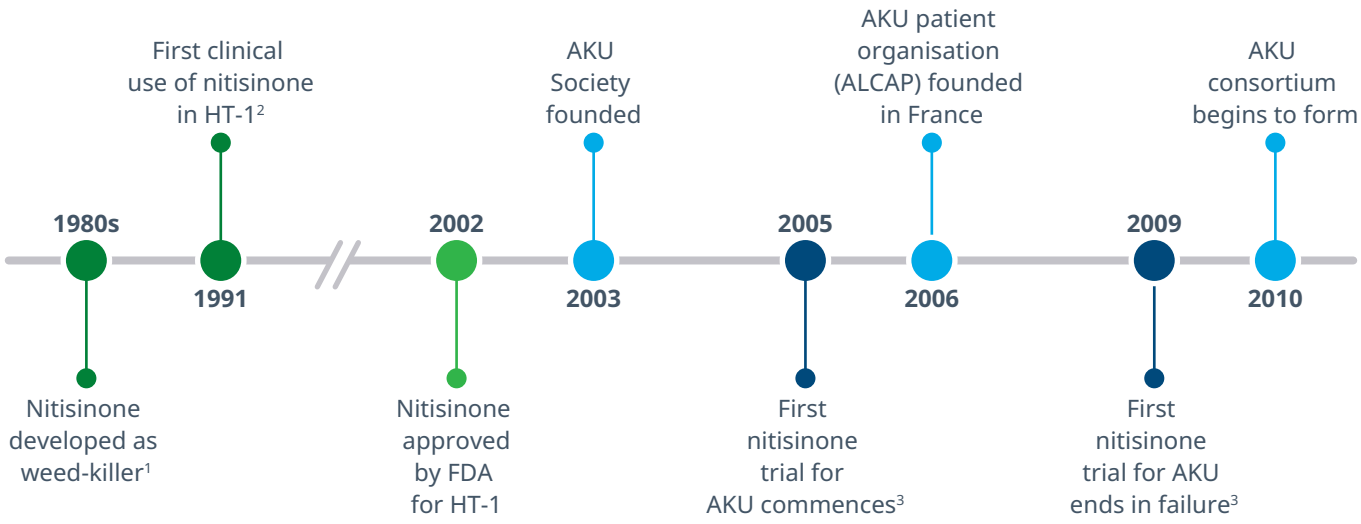
Identifying a potential treatment candidate

Nitisinone, the molecule that is now used to treat AKU, was first synthesised as a weedkiller after it was discovered that a closely-related substance, leptospermone, which is produced by the bottlebrush plant, prevents the growth of weeds. Subsequent

toxicology studies revealed that nitisinone affects the tyrosine pathway and as a result causes eye lesions in rats. A defect in this pathway is also responsible for the rare but lethal disease hereditary tyrosinemia type-1 (HT-1), which causes death at just a few months or years old, from liver failure, renal dysfunction, or liver cancer. In the early 1990s, nitisinone (at the time marketed under the brand name Orfadin by Swedish Orphan Biovitrum AB — Sobi) was successfully investigated as a treatment for HT-1 and was approved by the FDA and EMA in 2002 and 2005 respectively.[8]

Since a malfunction of the tyrosine pathway is also responsible for AKU, the National Institutes of Health (NIH) in the U.S. investigated nitisinone as a possible treatment. However, a three-year randomised trial involving 40 patients yielded inconclusive results and the development of the drug was not pursued further. In part, this was due to the trial design — because AKU progresses slowly, the timeframe was too short to determine treatment efficacy. With 40 patients, only half of those in the treatment arm and several dropouts, the trial was also underpowered. Lastly, the primary endpoint chosen (lateral hip rotation) was not reflective of the multiple ways in which AKU affects the body and the range of symptoms it produces. In patients with more advanced disease, joint damage may also no longer be reversible to a degree that would be considered statistically significant. It is noteworthy that biochemical results were promising, with a consistent 95% reduction of urinary and plasma homogentisic acid (HGA), the metabolite responsible for the tissue degradation which is the main feature of AKU. The trial also confirmed that nitisinone has generally very few side effects and adverse events.[9]

Figure 3: The path to a treatment part I



Sources: [1]https://www.ema.europa.eu/en/documents/scientific-discussion/orfadin-epar-scientific-discussion_en.pdf, [2]https://www.tandfonline.com/doi/full/10.2147/TACG.S113310,[3]A 3-year Randomized Therapeutic Trial of Nitisinone in Alkaptonuria - PMC (nih.gov)

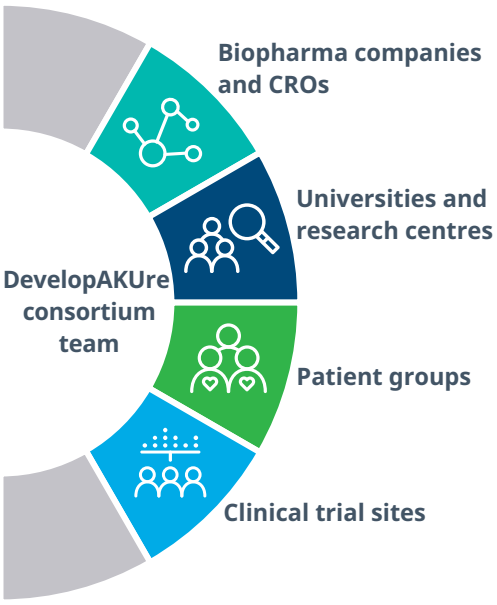
Establishing a research consortium

Due to the very nature of ultra-rare diseases, people living with the disease and their families often face major hurdles not only in dealing with healthcare providers who may not be familiar with the disease in question and how to manage it, but also in finding a community of others who are affected. This is often a significant driver for setting up a patient organisation, but identifying other patients and creating that community is also a considerable challenge. The AKU Society was set up in the UK in 2003 with just four known patients. The organisation started out by running a UK-wide identification campaign, which included contacting every GP, and succeeded in identifying approximately sixty patients in the UK. They then went on to identify people living with AKU in other European countries and encourage them to form their own organisations. As a result, a network of AKU patient organisations was established across many countries, including the Netherlands, Germany, Italy, Slovakia and France.

In 2010, in a bid to rescue nitisinone as an AKU treatment after the NIH study failed, the AKU Society began to push for a new research initiative based on the assumption that the failure of the previous study was due to trial design flaws rather than the efficacy of nitisinone, especially since those patients who had been able to access it as treatment spoke highly of it. The AKU Society worked on getting relevant stakeholders on board and eventually ended up forming a multi-national consortium involving patient organisations, researchers, research sites, and Swedish Orphan Biovitrum (Sobi), the manufacturer of Orfadin, the branded version of nitisinone.

The AKU Society had already established ties with Professor Lakshminarayan Ranganath, a founding member of the society, and Professor Jim Gallagher as well as the Royal Liverpool University Hospital. Sobi had little commercial interest in a further trial since Orfadin was set to lose market exclusivity shortly but agreed to support the proposed trial as a philanthropic initiative provided the AKU Society was able to secure funding, which they did. The EU provided a €6m grant and the AKU Society managed to raise a further €5m for the trial effort. In addition to the Royal Liverpool University Hospital, two further research sites joined the consortium, the Hôpital Necker & Institute Necker in Paris (France) and the National Institute of Rheumatic Disease (NURCH) in Piešťany (Slovakia). Last but not least, the network of AKU patient organisations provided an essential contribution in contacting, recruiting, and motivating patients to participate in the trial.[10]

Figure 4: 11 partner organisations across Europe



Swedish Orphan Biovitrum, Sweden
- Markets nitisinone (Orfadin®) and supplied these to DevelopAKUre
- Submitted data to the European Medicines Agency for approval
- Provided regulatory and pharmacovigilance support

PSR Group, Netherlands
- Medical monitor and trial manager for DevelopAKUre
- Submitted ethical and legal documents

University of Liverpool, UK
Led on sample analysis, data collection, data storage and statistical analysis of results

Nordic Bioscience, Denmark
Led on the analysis of several biomarkers indicating changes to the progression of AKU disease

Biomedical Research Centre, Slovakia
Led on sample analysis, data collection, data storage and statistical analysis of results

University of Siena, Italy
Led on analysis of biochemical samples, indicating inflammation and oxidative stress in samples taken from AKU patients

AKU Society, UK
- Initiated DevelopAKUre to assess nitisinone as a potential treatment for AKU patients
- Led patient identification, recruitment and support for all patients enrolled in clinical trials

Association pour la Lutte Contre l'Alcaptonurie, France
Led patient identification, recruitment and support for all patients enrolled in clinical trials at Hôpital Necker

National Institute of Rheumatic Disease, Slovakia
- Research and teaching centre in AKU, ochronosis and inflammatory rheumatic disease
- Slovak clinical trial site with ~80 patients

Royal Liverpool University Hospital, UK
- Assessment and treatment centre
- Budgeting and reporting to European Comission
- UK clinical trial site with ~100 patients

Hôpital Necker & Insitute Necker, France
- Experience with nitisinone for treatment of tyrosinaemia patient
- French clinical trial site with 33 patients

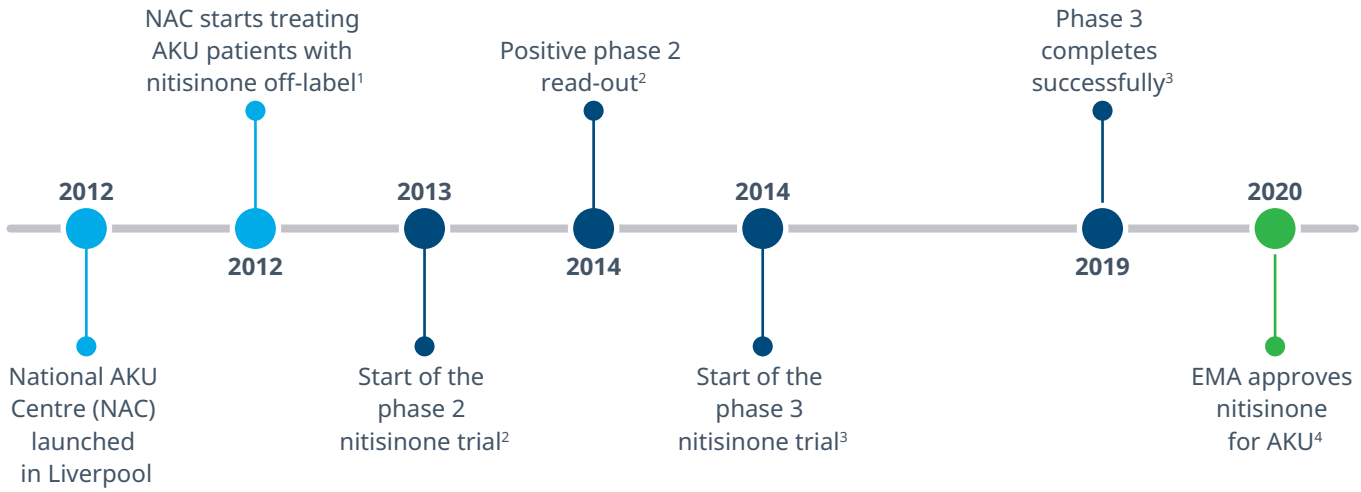
Trial planning, design, and execution

Crucial to the eventual success of the trials was careful planning and design, learning from the failure of the NIH trial, and soliciting timely advice from the EMA on study design. As a result of this discussion, it was decided to use HGA levels as the primary, and essentially surrogate, endpoint. The AKU Severity Score Index (AKUSSI) developed by Professor Ranganath, a composite measure for disease severity incorporating the clinical, joint, and spine domains was selected as the secondary endpoint. For the latter, the EMA did not demand statistical significance but only a positive trend.

As the phase one results from previous studies were adequate, the AKU consortium was able to move straight to phase two, which commenced in 2013.[11] After its successful completion, it was followed by a 4-year randomised phase three trial with 138 patients which in 2019 also concluded with very positive results. HGA levels in participants on the treatment arm decreased by 99.7% and the results for the AKUSSI demonstrated not only a positive trend, but also statistical significance.[12]

The EMA approved nitisinone as a treatment for AKU in 2020,[13] and the AKU consortium spent the subsequent two years securing HTA approvals. Sobi was the main driver of this process, bringing their market access expertise to bear. The AKU Society provided advocacy support where there were problems in getting regulators to fund the treatment.

Figure 5: The path to a treatment part II

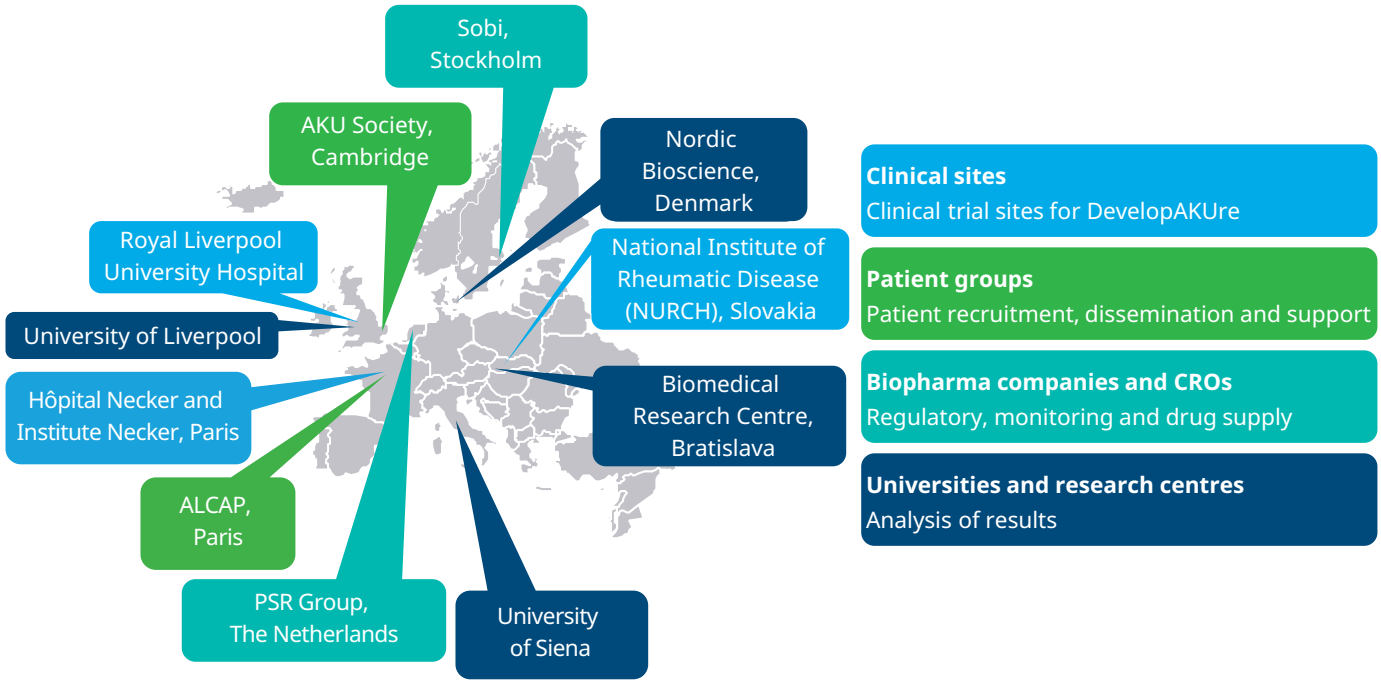


Source: [1]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9981412/,[2]https://www.sciencedirect.com/science/article/pii/S2214426922000064, [3]https://www.thelancet.com/journals/landia/article/PIIS2213-8587(20)30228-X/fulltext,[4]https://www.ema.europa.eu/en/medicines/human/EPAR/orfadin

Patient identification and recruitment

Identifying, recruiting, and retaining patients for clinical trials is a significant challenge and under-recruitment contributes to the overall decreasing performance of clinical trials.[14] This is even more the case for rare and ultra-rare diseases. Often the difficulty is not only in identifying patients but also making them aware of existing trials and enabling access. Some patient organisations play a decisive role in bringing patients and trials together, as for instance in the case of Duchenne UK.[15] Patient organisations are also ideally placed to understand patients' motivations for participating in trials and the obstacles they might face in doing so.

Figure 6: Geographic distribution of the consortium



Thanks to the early work of the AKU Society, there already was an existing network of patient organisations across Europe. These organisations were able to contact patients, provide information and education about the upcoming trial, and provide support and motivation throughout its duration. The three clinical trial centres recruited patients from beyond their respective countries: the Hôpital Necker (France) recruited from France and Belgium, the National Institute of Rheumatic Disease (Slovakia) from Slovakia and Jordan, and the Royal Liverpool University Hospital (UK) recruited patients from all over Europe. For ethical reasons, the Liverpool centre could not recruit patients from England and Scotland, because they had just set up the National AKU Centre (NAC) where UK patients could receive nitisinone off-label. These UK patients could not be recruited for the randomised clinical trial, where some of them would have been allocated to the non-treatment arm.

Enabling patient retention and providing support

Next to patient recruitment, patient retention is a major success factor for RCTs and prioritising support for trial participants and their carers is key here. Patient organisations are particularly well-placed to anticipate patient needs, develop solutions, and keep trial participants motivated since patient welfare is at their core, and the AKU consortium placed great emphasis on this aspect.

Patient motivation was a major factor and one which the AKU Society and its partner organisations prioritised from the start. Some patients had already participated in the unsuccessful NIH trial, in some cases on the non-treatment arm and were therefore likely to be already dispirited. The new trial also placed half of the participants on the non-treatment arm, and since nitisinone clears patients' urine, which in AKU sufferers turns black, trial participants would immediately know which arm they were on. It was especially important to convey to patients on the control arm how crucial these trials were, and in fact, altruism was a deciding factor for many patients' continued participation.

There were also more practical considerations: the EU funds covered trial participants' travel costs and the consortium took care of organising flights and accommodation for them. The consortium also raised an additional £100,000 to cover patients' carers' travel to Liverpool. There were also administrative issues. Patients had to cover some expenses themselves and then request reimbursement from the hospitals, which

often took considerable time. For many patients, this was a significant financial burden since many of them are low-income already due to their health issues and constituted a barrier to ongoing trial participation. The AKU Society stepped in and took over the reimbursement process, thus resolving this issue.

Lastly, the quality of the interaction between the research teams at the trial centres, the patient groups, and the trial participants was crucial. The trial centres ensured participants felt highly valued, and patients and patient groups were kept fully informed and up to date throughout the study. As a result, patient retention was high, with 108 of the 138 patients completing the study.[16]

Lessons learned and future outlook

Success factors

Two decades after the AKU Society was founded, and one decade after the AKU consortium was set up, they succeeded in making a life-changing treatment for AKU available to all patients in the EU and the UK. A number of factors made this achievement possible:

- **Robust trial design:** compared to the earlier U.S. trial, more suitable endpoints were used which more accurately reflected the effect of nitisinone on all patients including those in more advanced stages of disease. The AKUSSI score used as secondary endpoint also captures the wide range of symptoms of AKU in a way the earlier trial's singular endpoint had not. In addition, the European trials had a far higher number of participants (138 vs. 40) which improved the likelihood of statistically significant outcomes.
- **Early consultation with the EMA** ensured alignment on trial design and expectations for results.
- **Leveraging the existing patient organisation network** enabled the identification and recruitment of sufficient trial participants. The patient organisations provided information and education to their patient communities and especially helped those patients on the non-treatment arm of the trial to remain motivated.
- **Persistent patient focus** with attention given to making patients feel valued and included, and to removing practical obstacles to patients' participation in the trial.
- **Personal dedication and commitment** from the AKU Society but also other members of the consortium resulted in a network of strong working relationships and continued to drive the project forward. Consistent communication was also a key element.
- **Commitment from Sobi** despite lack of commercial incentives: although the branded version of nitisinone was set to lose market exclusivity, Sobi provided the drug to the trial participants and pitched in with their expertise in managing regulatory processes and market access. This was also driven by personal involvement of the then-CEO and the leadership team at the time.

Figure 7: Key success factors

Robust trial design: Suitable endpoints which reflected the effect of nitisinone on all patients including more advanced stages of disease and the wide range of symptoms of AKU and enough participants for statistical significance.

Early consultation with the EMA ensured alignment on trial design and expectations for results.

Persistent patient focus with attention given to making patients feel valued and included, and to removing practical obstacles to patients' participation in the trial.

Leveraging the existing patient organisation network to identify and recruit trial participants. Patient organisations provided information and education and helped patients to remain motivated.

Commitment from the pharma partner at the highest level of the organisation. They provided the drug and expertise in managing regulatory processes and market access.

Personal dedication and commitment from the consortium members resulted in a network of strong working relationships and continued to drive the project forward. Consistent communication was also a key element.

Looking ahead: towards a cure for AKU

While the development of this treatment represents a major milestone for AKU patients, nitisinone does have side effects. Most notably, it leads to a major increase in tyrosine and therefore requires patients to follow a restrictive low-protein diet. To mitigate this, the AKU Society is currently funding a research programme on the development of tyrosine inhibitors at the Royal Liverpool University Hospital. The ultimate goal however is the development of a cure for AKU and studies on mRNA and gene therapies are in the early stages. Funding is currently proving to be the biggest barrier.

Recommendations for creating a successful collaboration between patient organisations and pharma

As the example of the development of nitisinone as a treatment for AKU shows, patient organisations can be powerful drivers of drug development. Because of their personal involvement, they have an intimate understanding of the unmet needs of their patient communities as well as unrivalled access to these communities. They can provide invaluable input into trial design and understand how to genuinely prioritise patient concerns and needs. Their main limitations are usually financial.

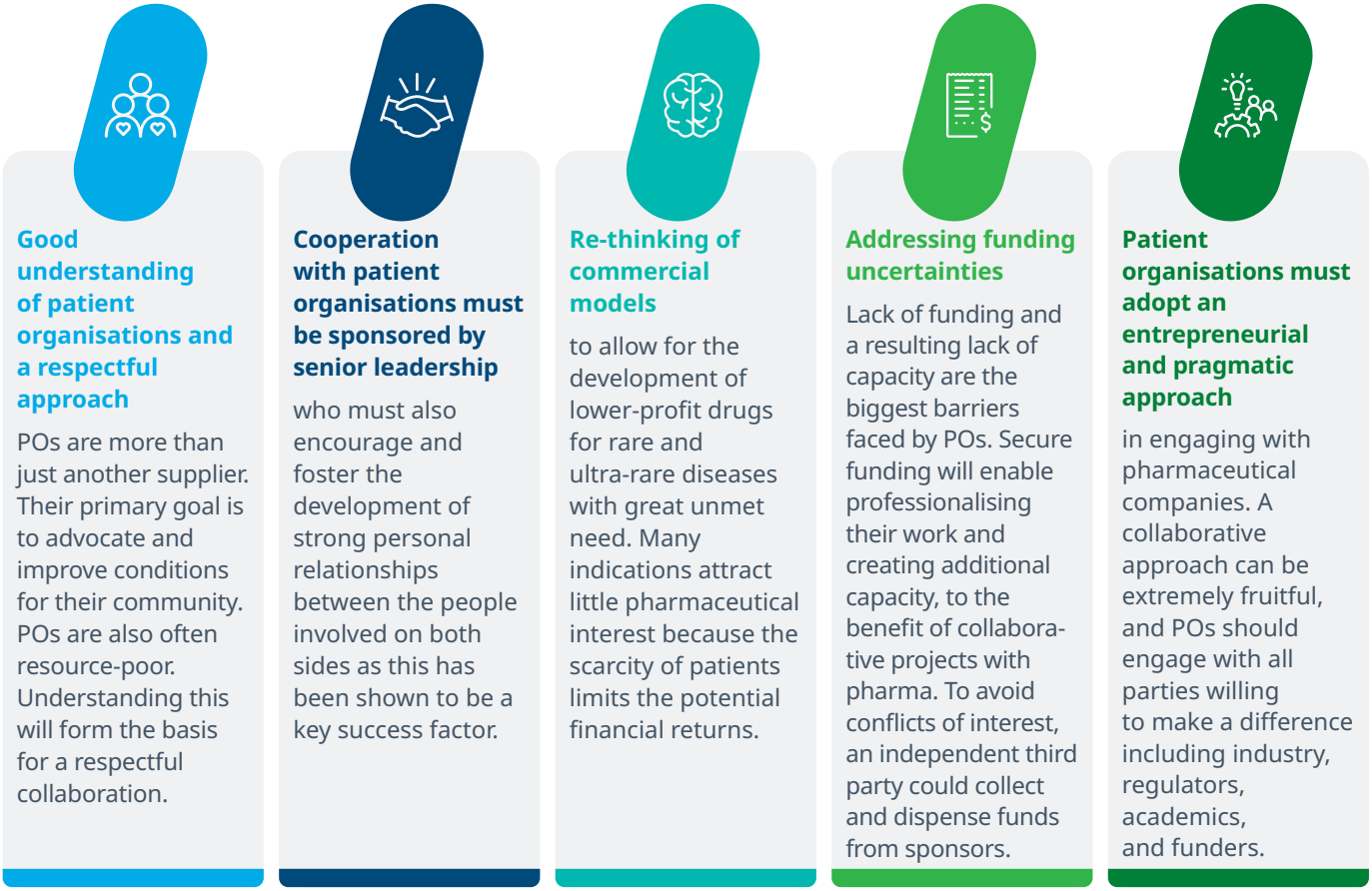
Especially in rare disease development, close alignment with patient needs and expectations is indispensable and patient organisations are able to provide this connection. For pharma companies, seeking out collaborations with patient organisations is therefore an advisable approach but requires careful and consistent management to succeed.

- **A good understanding of patient organisations and a respectful approach:** patient organisations are not just another supplier. Their primary goal is to improve conditions for people living with often debilitating diseases and their community. Especially in rare diseases, patient organisations are often

resource-poor. Typically, they are formed of parents or other family members who are trying to run the patient organisation in addition to caring for a family member, often a child, and juggling day-to-day responsibilities.

- **The cooperation with patient organisations must be sponsored by senior leadership.** It is also essential to develop strong personal relationships between the people involved on both sides. The good personal relationship between the CEO of Sobi and the head of the AKU Society was a key driver of the successful product development for AKU.
- **A re-think of commercial models** to allow for the development of lower-profit drugs for rare and ultra-rare diseases with great unmet need. Many indications attract little pharmaceutical interest because the scarcity of patients limits the potential financial returns.
- **Addressing funding uncertainties:** Lack of funding and a resulting lack of capacity are two of the biggest barriers faced by patient organisations for rare diseases. Since these groups operate at very low levels of funding and at the same time spend a lot of time and energy on fundraising, comparatively little can go a very long way in professionalising their work and creating additional capacity. This would also benefit the collaborative projects with the pharmaceutical industry. Since direct funding of patient organisations by pharma would inevitably create conflicts of interest, it has been suggested to set up an independent third party which could collect funds from sponsors and disperse them to relevant patient organisations.
- **Patient organisations must adopt an entrepreneurial and pragmatic approach** in engaging with pharmaceutical companies. Patient organisations can bring much to the table and provide the impetus for the development of treatments but ultimately the expertise in drug development and navigating market access and launch lies with pharmaceutical companies and CROs. As this case study shows, a collaborative approach can be extremely fruitful and patient organisations should embrace engagements with all parties willing to make a difference including industry, regulators, academics, and funders.

Figure 8: Creating a successful collaboration between patient organisations and pharma



Rare and ultra-rare diseases are an area with significant unmet need but also a great deal of development activity. While overall, R&D in rare diseases performs slightly better than R&D overall, there is considerable volatility reflecting the special challenges in this area. Cooperation between patient organisations and the pharmaceutical industry is a means of overcoming these challenges but requires a careful and respectful approach from the pharmaceutical industry and an entrepreneurial and pragmatic outlook on the part of patient organisations.

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